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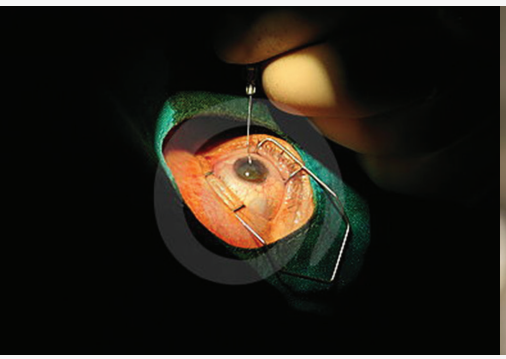
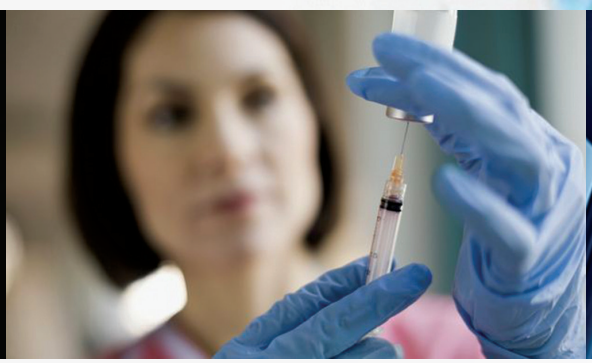


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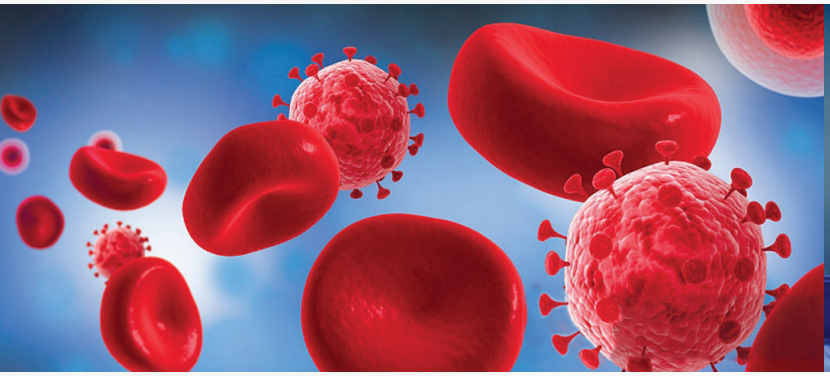
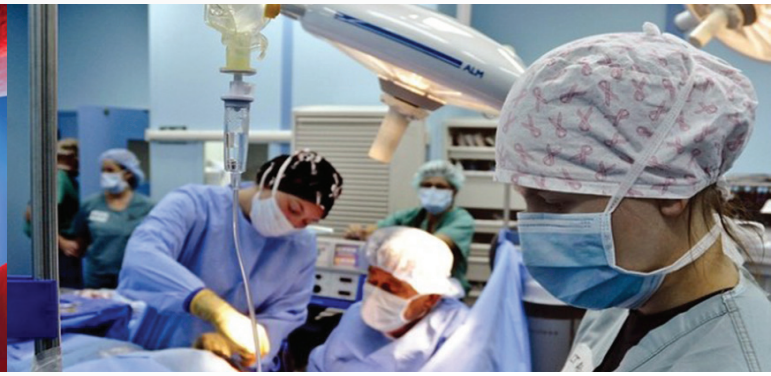

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Contents

EDITORIAL ASIAN JOURNAL OF MEDICAL SCIENCES

The science of "smell" and the noble for "hugs:" making "sense?"

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David Julius and Ardem Patapoutian were jointly awarded the 2021 Nobel Prize in Physiology and Medicine for their discoveries of receptors for temperature and touch.[1] It was a phenomenal moment for the scientific community, more for the discovery that forms the basic fabric of our everyday life—ever imagined how life would have been without feeling the aroma around? Or even the dangers of accidentally touching a heated object. Dr Julius and Dr Patapoutian, independently discovered key mechanisms of how living organisms sense heat, cold, and touch.[2] The journey started when Dr Julius, at the University of California, San Francisco, used a key ingredient in hot chili peppers to identify a protein in nerve cells that respond to these stimuli. Using capsaicin, the pungent component of chili peppers, he provided fundamental insights into mechanisms of pain.[3,4] Then using a meticulous cDNA library-based functional screening from sensory neurons to search for the gene(s) that could confer capsaicin sensitivity, Dr Julius identified for the first time a novel ion channel (now called transient receptor potential [TRP] vanilloid 1) belonging to the family of TRP ion channels associated with the pain sensitivity.[5,6] A painful exercise indeed!

While Prof Julius was exploring the oceans and skies to hunt for sensory pain pathways, quite independently, Dr Patapoutian of Scripps Research Institute La Jolla, California, was searching for a similar thing that seemed to bother him equally.[7] How do we sense touches? After all, there are so many emotions packaged in this small five-letter word, touch. The mother's touch is the first sensation that every single of us always cherishes. Dr Patapoutian research is centered around finding candidate genes in a mechanosensitive cell line that could respond to mechanical stimuli. After a thorough search, the team identified two mechanically-activated ion channels, PIEZO1 and PIEZO2, representing an entirely novel class of mechanical sensors-based ion channels.[8,9]

What is fascinating is the idea that discovery of the smell and touch receptor stretches far beyond just touch and temperature sensations only. Mutations in other TRP channels are involved in neurodegenerative disorders and skeletal dysplasia, while mutations in PIEZO channels help control critical functions such as respiration and blood pressure regulation.[10]

So now, the mysterious world surrounding us looks more transparent and clearer. The molecular landscape is defined with precision. We now have a chemical entity behind all these emotions and intuition. The warm hug that makes our day is now millions of ions crisscrossing the ion channels. There is a different side to this too. How will the world look if everything is defined as a chemical entity? Won't we lose the charm? After all, so much within the subtleness remains charmful when wrapped within the veil of ignorance. Knowing too much about something steals the show.

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ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

The effect of remdesivir on selective biomarkers and its value in predicting the clinical outcome in patients with COVID-19

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ABSTRACT

Background: To the best of our knowledge, there have been no studies to evaluate the effect of remdesivir on inflammatory markers. **Aims and Objectives:** To study the effect of Remdesivir on Selective biomarkers namely C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), Serum Ferritin and D-dimer and their value in predicting the clinical outcome in patients with COVID -19 infection. **Materials and Methods:** This is a retrospective observational study including 102 laboratory-confirmed COVID-19 patients of moderate and severe category who were subjected to complete blood count, liver function test, BUN, creatinine, C-reactive protein, lactate dehydrogenase, D-dimer, serum ferritin, ECG, and chest X-ray. The association was analyzed using independent sample t-test or Mann–Whitney U-test. Patients were divided into two groups. Both received corticosteroids and anticoagulants. Group A also received remdesivir. **Results:** Of the 102 patients, 90.2% of the patients in the non-remdesivir group and 94.1% in the remdesivir group were discharged. The mortality rate was 9.8% in the non-remdesivir group versus 5.9% in the remdesivir group (P = 0.71). There was no statistically significant difference in the decrease of the inflammatory markers overtime in both the groups, irrespective of whether they received remdesivir or not. **Conclusion:** High values of the inflammatory markers were seen at the time of admission. A 5 days course of remdesivir failed to demonstrate a statistically significant difference in the decrease in the levels of the inflammatory markers. However, we have observed a possible clinical benefit of remdesivir among patients with moderate and severe COVID-19 disease, as there was a trend toward better clinical outcomes. Further studies are needed to evaluate this therapeutic strategy.

Key words: COVID-19 infection; C-reactive protein; D-Dimer; Ferritin; Inflammatory markers; Lactate dehydrogenase; Remdesivir

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INTRODUCTION

The outbreak of COVID-19 has imposed a huge threat to global public health.[1] The spectrum of the disease severity ranges from mild asymptomatic disease to pneumonia leading to acute respiratory distress syndrome, multiple organ dysfunction, and even death.[1]

The rapid viral replication of SARS-CoV-2 and destruction of cells stimulate the inflammatory response and recruit macrophages which release cytokines, chemokines that attract immune cells leading to cytokine storm, subsequent multiorgan dysfunction, and death.[1]

Remdesivir a nucleotide analog targets the viral RNA-dependent RNA polymerase needed for the replication of SARS-CoV-2.[2] Thus, inhibiting the viral replication it inhibits the inflammatory response, and improves the clinical outcome.

Hence, early administration of remdesivir might be crucial for ensuring an efficient treatment, decrease in mortality, and an early discharge.

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Furthermore, there is accumulating evidence that the inflammatory responses play a critical role in the progression of COVID-19.[1,3-5] Hence, severe COVID-19 is associated with higher levels of inflammatory markers as compared to mild disease.

There have been no studies to evaluate the effect of remdesivir on inflammatory markers to the best of our knowledge.

Hence, this study has been undertaken to study the effect of remdesivir on selective biomarkers, namely, C-reactive protein (CRP), lactate dehydrogenase (LDH), serum ferritin, and D-dimer and their value in predicting the clinical outcome in patients with COVID-19 infection.

Aims and objectives

To study the effect of remdesivir on selective biomarkers, namely, C-reactive protein (CRP), lactate dehydrogenase (LDH), serum ferritin, and D-dimer and their value in predicting the clinical outcome in patients with COVID-19 infection.

MATERIALS AND METHODS

This is a retrospective observational study, which was pre-approved by the Institutional Ethics Committee. It included 102 laboratory confirmed COVID-19 patients of moderate and severe category between the age group of 18 and 60 years by RT-PCR on nasopharyngeal swab between August 1, 2020, and October 30, 2020, admitted in the Department of General Medicine of Vydehi Institute of Medical Sciences and Research Centre.

A detailed history comprising demographic characteristics, presenting complaints, and comorbidities was recorded, the patients then were categorized as mild, moderate, and severe disease based on the clinical criteria according to the Karnataka Government guidelines of August 2020. Category B (moderate) patients were those who had the features of respiratory rate 24–30/min, SpO_2 90–94% at room air. Category C (severe) patients were those who had the features of respiratory rate >30/min, SpO_2 <90% at room air or <94% with oxygen, acute respiratory distress syndrome, or septic shock. In addition to examination, all the patients were subjected to complete blood count using DXH-900 automated hematology analyzer with six part differentials, liver function test using Beckman Coulter Unicel DXC 800 Synchron Clinical system, blood urea nitrogen by urease UV method, creatinine by Jaffe's kinetic method, CRP by Nephelometry method, LDH by lactate to pyruvate method, D-dimer by latex immunoassay and serum ferritin levels by Clinical Laboratory Improvement Amendments method, ECG, and chest X-ray. Both the groups received corticosteroids and anticoagulants. In addition, Group A received intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–5 in single daily infusions) as per Karnataka Government Treatment protocol and Group B did not receive intravenous remdesivir. The patients excluded from the study were category A (mild) patients with respiratory rate <24 cycles/min, SpO_2 >94% in room air; patients with pre-existing comorbidities, namely, chronic liver disease, chronic kidney disease, malignancy, thromboembolism, diabetes mellitus, hypertension, ischemic heart disease, chronic lung disease, sepsis, anemia, pregnant women, and children.

Statistical analysis

Statistical analysis was carried out for the laboratory confirmed moderate to severe COVID-19 patients.

The association was analyzed using independent sample t-test or Mann–Whitney U-test.

Microsoft Excel 2013 and Statistical Package for the Social Sciences Version 19.0 software were used for data entry and analysis.

$P<0.05$ will be considered as statistically significant.

Informed consent has been waived off as it is a retrospective study.

RESULTS

In this study, we had a cohort of patients that did not receive remdesivir and those that did. The first 51 patients in each group were selected the non-remdesivir group (Group A) and remdesivir group (Group B) for the study.

The median age of patients was 42 years in Group A and 41 years in Group B with a majority of the patients being males, 80.4% in Group A and 76.5% in Group B (Table 1).

Table 1: Patient Characteristics and outcome

Variables	Remdesivir N (%)	
	Not received	Received
Age (Median Q_1, Q_3)	42 (35.55)	41 (33.50)
Gender		
Male	41 (80.4)	39 (76.5)
Female	10 (19.6)	12 (23.5)
Severity		
Moderate	44 (86.3)	30 (58.8)
Severe	7 (13.7)	21 (4.2)
Outcome		
Discharged with government protocols	46 (90.2)	48 (94.1)
Mortality	5 (9.8)	3 (5.9)

In the non-remdesivir group, 86.3% had moderate illness and 13.7% had severe illness. Whereas, in the remdesivir group, the patients with moderate and severe disease were 58.8% and 41.2%, respectively (P=0.002) (Table 1).

Correlation of inflammatory markers between the groups (Table 2)

The inflammatory markers, namely, D-dimer, ferritin, LDH, and CRP were serially monitored in all patients on day 1, day 3, and day 5 of hospital admission. These markers were seen to be higher at presentation (day 1) in the non-remdesivir group as compared to the remdesivir group (Table 2).

There was a significant decrease in the mean ferritin (P<0.001) and LDH (P=0.001) values over these time points in both the groups, irrespective of whether they received remdesivir or not (Table 2).

There was no statistically significant difference in the decrease in the mean values of any of the inflammatory markers between the two groups (Table 2).

Clinical outcome

In our study, 90.2% of the patients in the non-remdesivir group and 94.1% in the remdesivir group were discharged. The mortality rate was 9.8% in the non-remdesivir group versus 5.9% in the remdesivir group. Fisher's exact test was performed to see the association between outcome and group. This difference was not found to be significant (P=0.71) (Table 1). There was a significant decrease in the mean ferritin (P<0.001) and LDH (P=0.001) values overtime in both the groups, irrespective of whether they received remdesivir or not. A 5 days course of remdesivir failed to demonstrate a statistically significant difference in the decrease in the levels of the inflammatory markers.

DISCUSSION

In our study of 102 patients, it was observed that men had a significantly higher rate of hospitalization as compared to women which is in agreement with other studies done by Gomez et al., and Bischof et al.[6,7]

Our study also showed, 90.2% of the patients in the non-remdesivir group and 94.1% in the remdesivir group were discharged. The mortality rate was 9.8% in the non-remdesivir group versus 5.9% in the remdesivir group.

Our findings corresponded with the ACTT-1 trial, which is an multinational study of 1062 patients where the patients were randomized in a 1:1 ratio to receive remdesivir or placebo showed that the recovery time among the remdesivir group was shortened by 5 days (P <0.001) and a lower mortality rate among the remdesivir group which was not statistically significant.[8]

Furthermore, a study by Mehta et al., showed mortality benefit with initiation of remdesivir ≤9 days from symptom onset which reinforced the need for appropriately timed remdesivir in moderate-to-severe COVID-19.[9]

Our study showed high levels of inflammatory markers, namely, D-dimer, ferritin, LDH, and CRP among the patients who were categorized among the moderate and severe illness category on admission.

This was similar to results of a meta-analysis comprising 3962 patients done by Zeng et al., which showed higher levels of CRP, LDH, procalcitonin, and serum ferritin among the severe illness patients as compared to the mild illness patients.[1]

A meta-analysis by Ghahramani et al., also showed higher levels of inflammatory markers among the severe group versus non-severe group.[10]

Table 2: Correlation of inflammatory markers between the groups

Variables	Group	Day 1	Day 3	Day 5	P value (between groups)	P value (between time)
D-dimer	Remdesivir	1236.33±2089.19	1362.51±2358.57	1300.08±2165.98	0.39	0.33
	Not received	802.65±882.35	1189.80±1839.76	1211.63±1925.07		
Ferritin	Received remdesivir	742.76±459.95	726.63±407.52	679.28±311.11	0.24	0.001 Day 1 vs. Day 3: 0.78 Day 1 vs. Day 5: 0.002* Day 3 vs. Day 5: 0.005*
	Not received	695.07±435.44	655.06±354.87	553.41±304.33		
LDH	Remdesivir	335.41±149.84	333.77±132.92	307.35±127.87	0.24	0.001* Day 1 vs. Day 3: 1 Day 1 vs. Day 5: 0.001* Day 3 vs. Day 5: 0.008*
	Not received	316.90±87.87	314.33±82.36	280.12±73.10		
CRP	Remdesivir	6.79±6.26	5.95±6.06	5.97±6.21	0.11	0.05
	Not received	5.98±4.54	4.81±4.63	3.98±5.32		

CRP, a hepatic protein which is regulated at the transcriptional level by the cytokine IL-6 and IL-1, is a reliable marker of inflammation.[11] There is accumulating evidence that higher levels of CRP are associated with severe COVID-19 infection.[12-14]

Our study showed that patients with moderate and severe COVID-19 infection had high values of CRP in moderate and severe COVID-19 infection at the time of admission. However, there was no statistical difference in the reduction of the CRP values among the patients who received inj. remdesivir.

Our findings were similar to a study by Smilowitz which showed that higher levels of CRP were associated with critical illness and mortality in COVID-19 patients.[15]

Similarly, a study of 131 patients showed persistently rising values of CRP was associated with higher levels of mortality among COVID-19 patients.[16]

D-dimer, formed by the activation of the plasmin enzyme, indicates the presence of broken-down fibrin in the bloodstream and represents the activation of coagulation and fibrinolysis systems.[17] Studies have indicated that higher levels of D-dimer were associated with more severe disease due to various reasons like increased levels of pro-inflammatory cytokines, thrombosis leading to venous thromboembolism and severe sepsis which leads to increased levels of plasminogen activator inhibitor 1, and excessive fibrinolysis.[18]

Our study showed that patients with moderate and severe COVID-19 infection had high values of D-dimer at admission. However, there was no statistical difference in the reduction of the D-dimer values among the patients who received inj. remdesivir.

Our findings were in agreement with a meta-analysis of 1807 patients done by Paliogiannis which revealed that higher D-dimer levels were associated with more severe COVID-19 infection as compared to non-severe infection.[19]

Similarly, a study done by Huang et al., on 676 revealed that a persisting increase in D-dimer levels was associated with higher incidence of mortality in COVID-19 patients.[20]

LDH, an intracellular enzyme, is found in cells in almost all organ systems, and it catalyzes the interconversion of pyruvate and lactate, with concomitant interconversion of NADH and NAD^+.[21] Isoenzyme 3 of LDH is present in lung tissue. Hence, greater levels of LDH are seen in patients with severe COVID-19 infection who have severe interstitial pneumonia, often evolving into acute respiratory distress syndrome.[22]

Our study showed that patients with moderate and severe COVID-19 infection had high values of LDH on admission. However, there was statistical decrease in the reduction of the LDH values among the patients irrespective who received inj. remdesivir.

Similarly, a study by Henry et al., showed that higher levels of S. LDH were associated with 6 times higher risk of developing more serious infection and 16 times increase in the odds of mortality.[22]

Furthermore, a study done by Martha on 10,399 showed a higher probability of worse outcomes in patients with COVID-19 infection.[23]

Ferritin in COVID-19 is characterized as an acute-phase reactant, as well as a mediator of immune dysregulation. Several complex feedback mechanisms between ferritin and cytokines exist in the control of pro-inflammatory and anti-inflammatory mediators. Cytokines induce the expression of ferritin. Furthermore, ferritin can induce the expression of pro- and anti-inflammatory cytokines.[24]

Our study showed that patients with moderate and severe COVID-19 infection had high values of ferritin in COVID-19 infection. However, there was statistical decrease in the reduction of the serum ferritin values among the patients irrespective who received inj. remdesivir.

A study done by Bo Zhou on 20 patients of COVID-19 patients showed higher levels of serum ferritin among patients with severe disease.[25]

Similarly, a study by Onur et al., showed high values S. ferritin among the non-survivors.[26]

Hence, higher levels of serum ferritin can be associated with severe COVID-19 infection.

Limitations of the study

To begin with our study is a retrospective analysis. Furthermore, the duration of follow-up was relatively short (5 days). Following up on inflammatory markers for a week after completing the course of remdesivir could have shown a difference between the groups. Furthermore, there is inhomogeneity in the groups studied with higher number of severe cases in the remdesivir group. Finally, we were not able to get a statistical analysis in the remdesivir subgroup due to very few patients with severe disease in the non-remdesivir

group. Probably looking at moderate and severe illness separately would be more conclusive.

CONCLUSION

High values of the inflammatory markers were seen among the moderate and severe illness patients at the time of admission. A 5 days course of remdesivir failed to demonstrate a statistically significant difference in the decrease of the levels of the inflammatory markers. However, we have observed a possible clinical benefit of remdesivir among patients with moderate and severe COVID-19 disease, as there was a trend toward better clinical outcome among the patients receiving remdesivir. Further studies are needed to evaluate this therapeutic strategy.

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PROFORMA

Code number: Date of admission:
Age: Date of Discharge:
Sex: Hospital number:
COVID RT-PCR:
Co-morbidities:
Severity of the illness at presentation (Based on clinical parameters): Mild/Moderate/Severe
Biomarkers:

	First test	Second test	Third test	Fourth test	Fifth test
	Day 1	Day 3	Day 6	Day 9	Day 12
Serum ferritin					
CRP					
LDH					
D-dimer					

Remdesivir: Not Received/Received
Oxygen requirement: Yes/No Number of days:
Ventillator requirement: Yes/No Number of days:
Days of ICU stay:
Days of Hospital stay:
Condition at discharge:

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ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Trends of variation of the laboratory parameters during the course of COVID-19 Illness

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ABSTRACT

Background: The coronavirus pandemic which had its origin in the Wuhan China has been spreading across the globe with far reaching complications and a variable clinical course. A variation of the laboratory parameters during the disease course remains a constant parameter to monitor the disease course and progression. Since the laboratory parameters are standardized globally, these may also act as uniform guidelines for the patients monitoring and treatment. **Aims and Objectives:** The aim of the study was to serial charting of the laboratory parameters in the recovered and expired patients of COVID-19 and to determine an associated prognostic significance. **Materials and Methods:** A retrospective observational study from the laboratory and medical records was conducted on the patients admitted from March 17, 2020, to May 31, 2020, at the tertiary care center dedicated to the treatment of RT-PCR confirmed COVID-19 positive patients. **Results:** The group of parameters showing a poor prognosis include a rising WBC count, high neutrophilic percentage, low lymphocyte percentage (<10) an NLR > 15, low lymphocyte monocyte ratio < 3, rising blood urea nitrogen, serum creatinine levels, and serum electrolyte levels. The liver function tests variation reflecting a poor metabolic activity of the liver, namely, a low serum albumin and albumin globulin ratio, rising SGOT levels, and total bilirubin levels. A highly significant variation in the acute phase reactants showing an exponential rise such as the serum lactate dehydrogenase levels, serum ferritin, fibrinogen, C-reactive protein, and IL 6 levels an increased level of D Dimer (>3) and a prolongation of the APTT. **Conclusion:** The variation of the laboratory parameters acts as a fair marker for the disease progression. Since the disease shows a variable progression with a sudden worsening of the clinical symptoms, a comprehensive monitoring of the laboratory parameters serves to diagnose and treat the disease progression.

Key words: COVID-19; Laboratory parameters; Comparison

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INTRODUCTION

The coronavirus pandemic has been spreading across the globe with far reaching complications and a variable clinical course. While the virus presents with varying clinical presentation with each wave, the variation of the laboratory parameters during the disease course helps to monitor the disease course and progression.

Aims and Objectives

1) To study the variation of the laboratory parameters from the hospital records of the patients admitted to a tertiary care hospital dedicated to the treatment of the patients with a Corona Virus infection as confirmed by a positive RT PCR test.
2) To analyze the variation of the laboratory parameters amongst the recovered & the expired patients.

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MATERIALS AND METHODS

A retrospective observational study from the laboratory and medical records was conducted on the patients admitted from March 17, 2020, to May 31, 2020, during the first wave of the disease, at the tertiary care center dedicated to the treatment of RT-PCR confirmed COVID-19 positive patients, after obtaining the institutional review board approval on June 10, 2020. Out of a total of 2739 patients admitted, consecutive 241 expired and 530 recovered patients were shortlisted of which 39 expired and 47 recovered patient's data were analyzed, after applying the inclusion and the exclusion criteria and their data. The statistical analysis was done using software SPSS 20.0 from IBM.

Machines and reagents

The routine blood tests and the biochemistry parameters and the acute phase reactants were carried out on the Siemens ADVIA – 2120, SIEMENS ADVIA 1800, Mindray BS- 200 and SIEMENS ADVIA Centaur XPT automated biochemistry analyzer, respectively.

RESULTS

The mean age of the patients was 62.62 (±14.42) and 37.83(±14.71) years, with a M: F ratio of 4:1 and 2:1 in the expired and the recovered patients, respectively, (Table 1, Figure 1a and b).

A progressive rise in the total WBC count and the neutrophil percentage, a decline in lymphocyte percentage and a lower monocytes percentage, along with a low lymphocyte monocyte ratio (LMR <3) and high neutrophil lymphocyte ratio (NLR >3) in the expired patients (Figure 2a). An insignificant variation in the levels of hemoglobin, platelets, RDW, and hematocrit levels was seen (Figure 2b).

High blood urea nitrogen (BUN), serum creatinine levels, and serum electrolytes were seen in the expired patients with a significant variation (Figure 3).

Serum albumin globulin ratio, serum albumin levels, total serum protein, alkaline phosphatase, serum aspartate transaminase (AST), and the total bilirubin were high with a significant variation (Figure 4a and b) while direct bilirubin,

Table 1: Variation of parameters during the disease and its significance

Parameters	Early	Middle	Late	P-value
Total WBC			>15000	<0.00001
Neutrophil %			>85	<0.00001
Monocytes%			<5	0.006
Lymphocytes %			<10	<0.00001
LMR			<2	<0.00001
NLR			>15	<0.00001
RDW			>15	0.73
Hct				0.20
Hb				0.055
Platelets				0.98
BUN			> 110	<0.00001
Se Creatinine			> 2	<0.00001
Se Sodium	Constant			0.007
Se Potassium	Constant			<0.00001
Se Chloride				0.96
Total Bilirubin				0.002
SGPT/ALT	>80			0.10
SGOT/AST	>110			0.043
Se Protein			<5.7	0.005
Alb:Glo ratio			<1.5	<0.00001
Se Globulin				0.204
Indirect Bilirubin				0.209
Direct Bilirubin			>0.3	0.376
Se Alk Phosphatase			>145	0.002
Se Albumin			<3.1	0.0001
IL6	>500			0.33
Se Ferritin		>950 (>3×)		<0.00001
LDH			>600 (>3×)	0.0001
CRP			>55 (>90×)	0.027
Troponin C	>20 times			0.085
D Dimer	>3			0.019
APTT		>50		< 0.00001
Fibrinogen			>900 (>2×)	< 0.00001

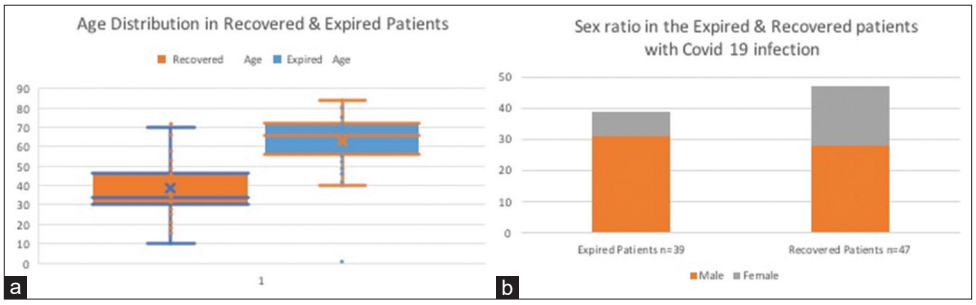

Figure 1: (a) The expired patients had a higher age distribution (median 66 years) compared Recovered patients (median 34 years). (b) The expired patients had a higher M:F sex ratio being 3.87:1 compared to 1.47:1 in the recovered patients

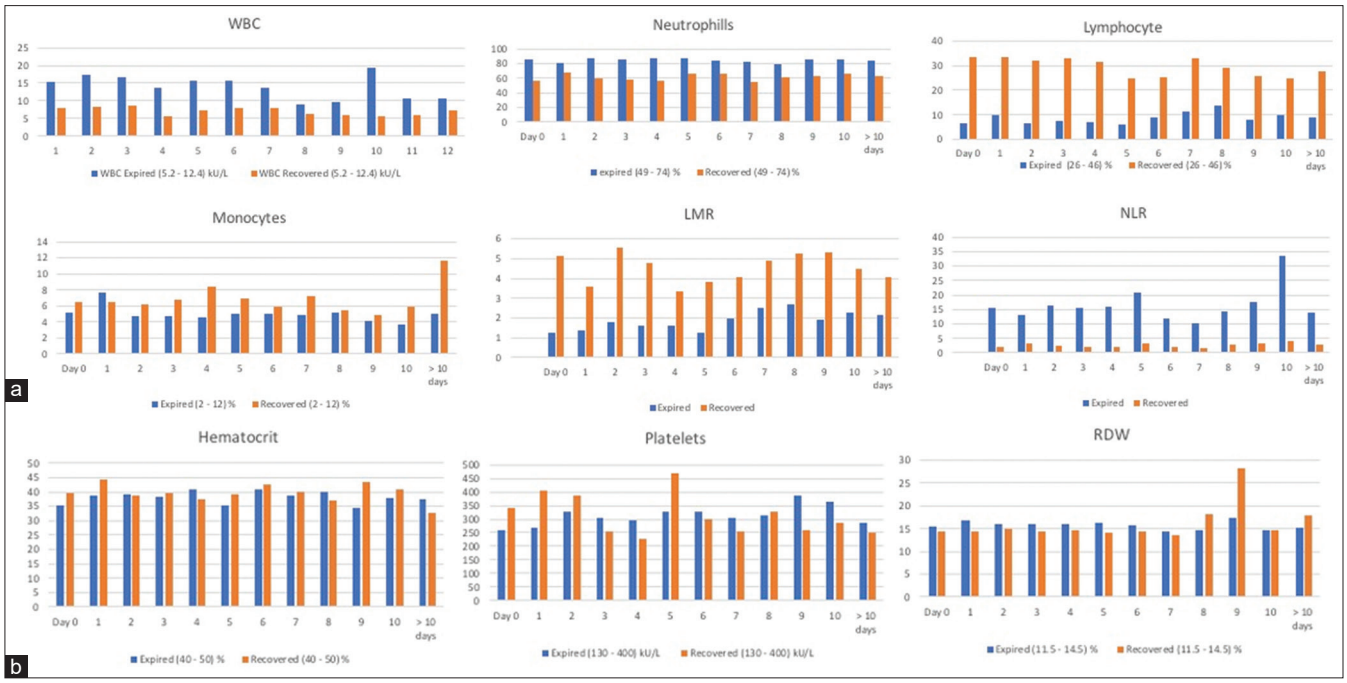

Figure 2: (a) A statistically significant variation was seen in the levels of total WBC, high neutrophil, low lymphocyte and lower monocytes levels with a significant variation in the LMR (<3) and the NLR ratio and a lower Hemoglobin levels in the expired patients. (b) The hematocrit levels, platelet levels and the RDW show a statistically non-significant variation, although a low hematocrit and higher RDW was seen in the expired patient

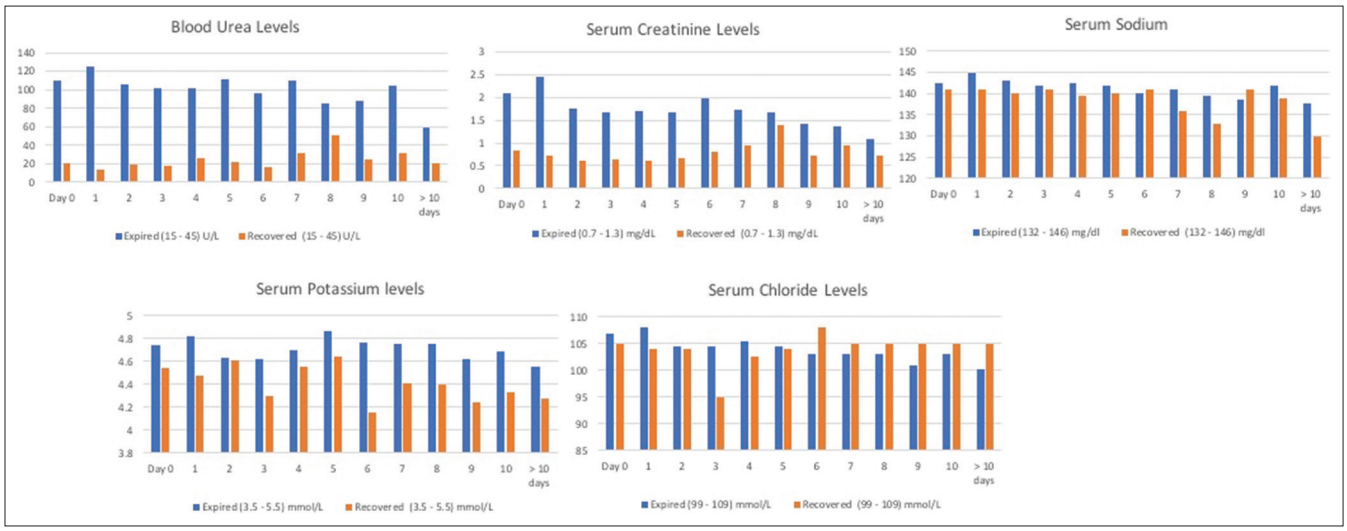

Figure 3: Renal function tests. The blood urea and serum creatinine levels and the serum electrolytes showed a statistically significant variation, with an increased level in the expired patients increasing more towards the terminal disease phase

serum globulins, and serum alanine transaminase showed an insignificant variation.(Figure 4c).

Serum ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), and serum fibrinogen levels showed a highly significant variation (Figure 5).

A highly significant variation was seen in the D dimer and APTT levels (Figure 6).

DISCUSSION

The worldwide trend of age distribution pattern in COVID-19 positive patients ranges from a mean of 40–60 years.[1-3]

An increased WBC count and neutrophils percentage along with a reduced lymphocyte and platelets counts in severe and fatal COVID-19 disease.[2,4,5] A few studies reported a low WBC count in the disease.[6-8]

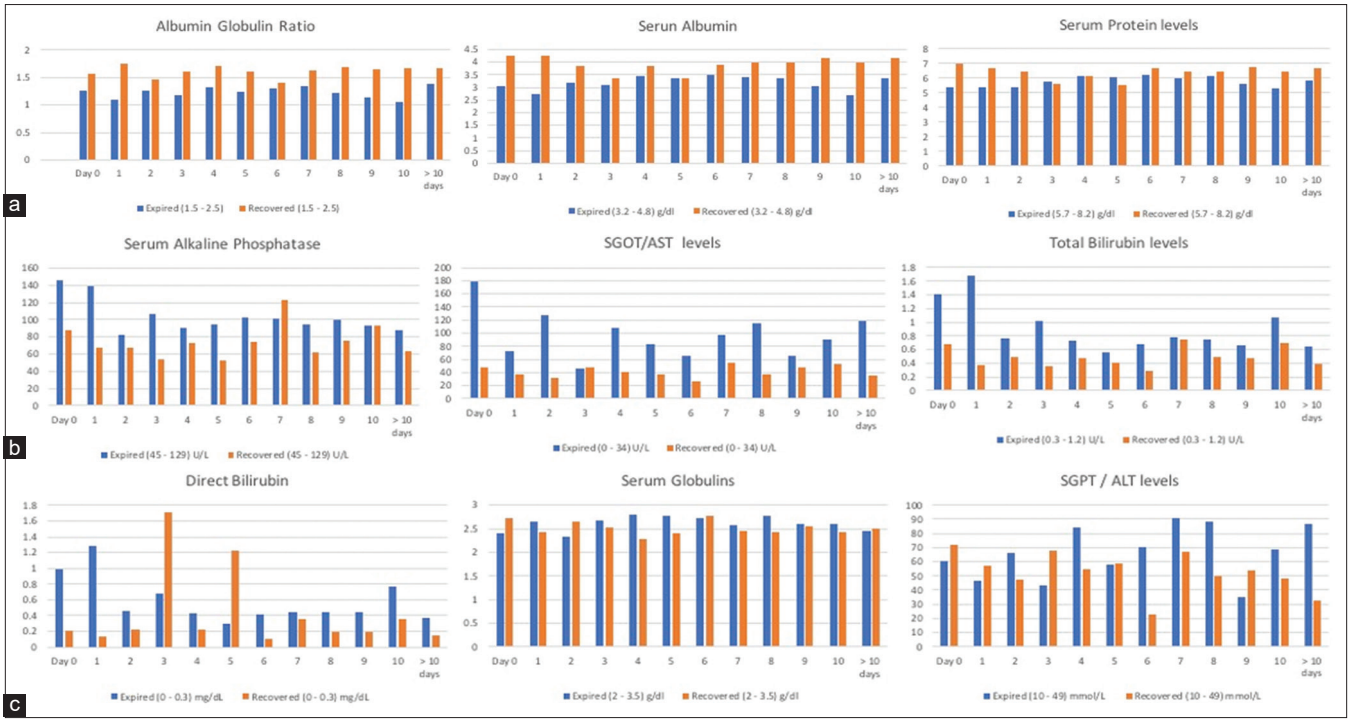

Figure 4: (a) A highly significant statistical variation was seen in the albumin globulin ratio, serum albumin levels and total protein levels, particularly in the imminent terminal disease phase in the expired patients. (b) The liver enzymes including the alkaline phosphatase and sgot along with the total bilirubin levels showed a significant statistical variation, with a consistently higher levels of the enzymes in the imminent terminal disease phase in the expired patients. (c) No significant statistical variation in the levels of Direct Bilirubin, Serum globulins and SGPT levels was seen

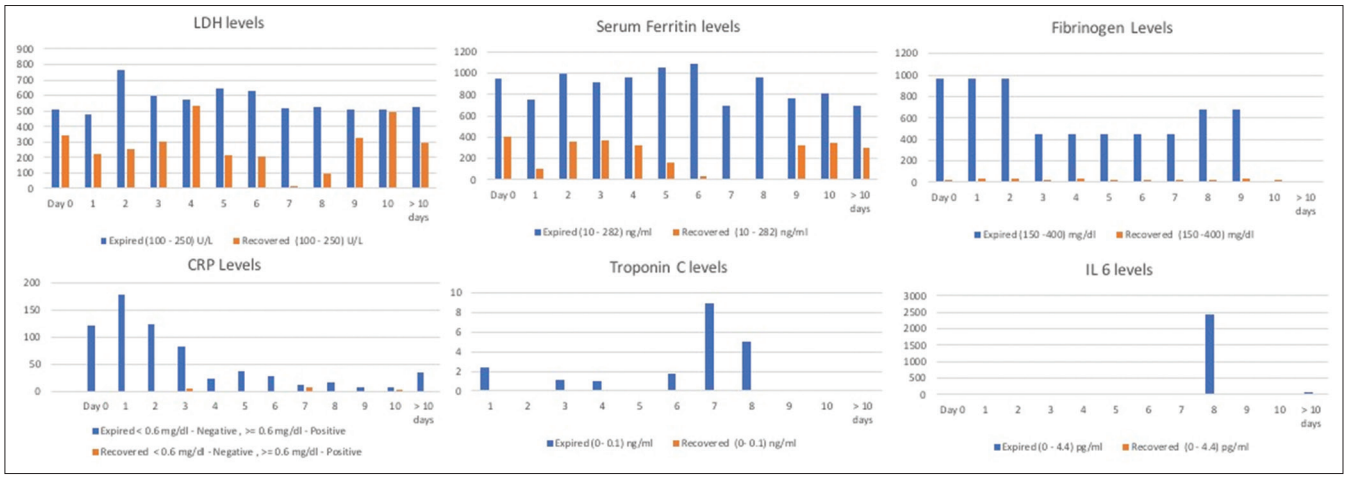

Figure 5: Variation of acute phase reactants. An exponential rise in the levels of serum LDH, serum ferritin, fibrinogen, CRP and IL6 levels was seen in the expired patients

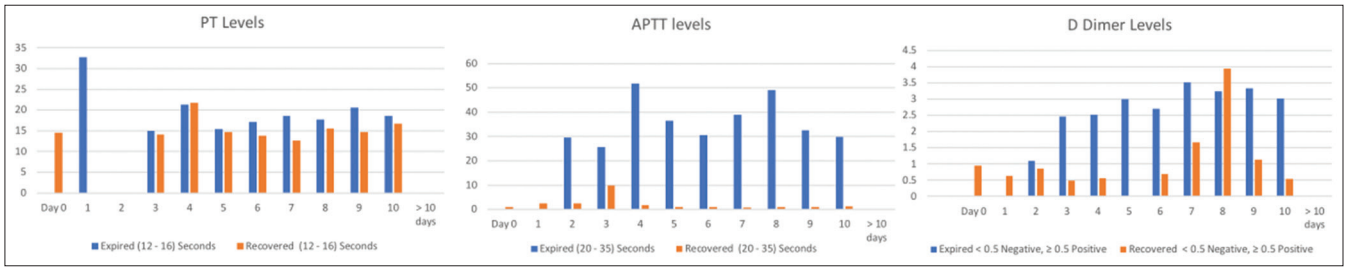

Figure 6: Variation in D-dimer levels and coagulation profile. A Dimer level of >3 was seen early in the disease in the expired patients, along with an increased value of APTT

Various studies observed a falling lymphocyte count with an increasing disease progression,[9,10] more significantly a lymphocyte percentage of less than 5% was associated with a poor prognosis,[11] along with a repletion of lymphocytes as an important factor for recovery.[12]

An expansion of monocyte population in the ICU bound patients was seen[7] which differs from a low monocyte count observed in our study.

Although no studies comparing the variations in the values of RDW and hematocrit in COVID-19 patients were found, RDW variations during other viral diseases (liver failure in HEV)[13] and poor prognostic marker in various diseases was found.[10-12]

There was no significant variation in the platelet levels in various studies.[1,13,14]

Various studies indicate the importance of an acute renal damage and its association with mortality in COVID-19 particularly during the late disease course,[15-21] whereas other studies showed a relatively low incidence of AKI in COVID-19.[22,23]

The liver enzymes were found to be altered in various studies, particularly in severe COVID-19 disease.[24-28]

A transient and mild variation of the liver function tests was mentioned in other studies with no significant relation to disease severity.[29,30]

A higher levels of the acute phase reactants were seen in more severe disease and in the expired patients than the survivors in a large number of studies.[31-38] with a particular emphasis on the association of LDH, and creatinine as the variables most predictive of respiratory failure, whereas maximal IL-6 level showed the strongest association with the need for mechanical ventilation, followed by maximal CRP level.[11,38-41] An analysis of cardiac makers revealed a much higher indicated a higher fatality risk associated with abnormal myocardial parameters.[42]

A higher threshold for D-dimer was found to be associated with an increased risk of pulmonary embolism and other complications in COVID-19 patients.[43-47]

A high admission D-dimer levels, and increasing D-dimer trends associated with a significantly greater risk of all-cause mortality were reported in various studies.[44,48-51]

Limitations of the study

The study was conducted on the patients admitted to the hospital in a relatively small cohort of patients. This might represent the variation of results in a selective patient population who have an access to the medical care.

CONCLUSION

We conclude that a highly significant variation was seen in hematology parameters, renal function tests, acute phase reactants, and the coagulation profile in the expired patients. The parameters showing a significant association with the disease progression include

1. Hematology profile with a high WBC count with rising NLR (>3), reduced LMR (<3) with falling lymphocyte percentage along with a borderline low hematocrit and high RDW
2. A significantly altered renal profile with rising BUN and serum creatinine levels
3. An alteration in the liver functions with lower albumin and total protein levels and rising liver enzymes and serum globulin levels
4. Rising levels of acute phase reactants including serum fibrinogen, CRP, and LDH along with an altered coagulation profile with rising D Dimer levels.

Since the disease shows a variable progression with a sudden worsening of the clinical symptoms, a comprehensive monitoring of the laboratory parameters serves to diagnose and treat the disease progression.

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ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

A comparative study of the efficacy and outcome of methylprednisolone and dexamethasone in moderate to severe COVID-19 disease

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ABSTRACT

Background: COVID-19 disease is caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). In the first half of 2020 COVID-19 disease has already converted into a global pandemic. Many treatment options were explored through the world. **Aims and Objectives:** To compare the efficacy and outcome of methylprednisolone (MTP) and dexamethasone (DEXA) in moderate-to-severe COVID-19 disease. **Materials and Methods:** In this prospective study, a total of 140 moderate to severe COVID-19 patients were enrolled from 15 April to June 15, 2021. These patients were randomly allocated into two groups, 70 patients were received MTP 2 mg/kg/day for 3 days followed by 1.0 mg/kg/day for 3 days in divided doses while 70 patients received DEXA 8 mg/day in divided dose up to 10 days. **Results:** The mean age was 45.5 years in MTP group whereas 45.34 years in DEXA group. The clinical outcome in MTP group and DEXA group was assessed in terms of clinical improvement (92.85% vs. 81.42%), radiological improvement (82.85% vs. 68.57%), transfer to ICU (5.71 vs. 14.57%), needs of ventilatory support (2.85% vs. 8.57%) and mortality (7.14% vs. 18.57%) respectively. **Conclusion:** In this study, MTP demonstrated better outcome as compared to DEXA in COVID-19 patients.

Key words: COVID-19 disease; Dexamethasone; Methylprednisolone

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which causes coronavirus diseases (COVID-19) was first identified in December 2019 in Wuhan city, China, and later spread to many provinces in China[1] and has spread with great speed around the world.

On March 12, 2020, it was declared as global pandemic by the World health organization.[2] The first SARS-CoV-2 positive case in India was reported in the state of Kerala on January 30th, 2020.[3]

The COVID-19 primarily affects the lung resulting in inflammation and pneumonia. On the basis of clinical, biochemical, and radiological parameters it is divided into mild, moderate, and severe disease. In mild disease, there is fever and upper respiratory symptoms but no documented hypoxia or shortness of breath. In moderate disease, there is tachypnea >24/min, hypoxia (Spo_2 <93%), and in severe disease there is tachypnea >30/min, hypoxia (90%), and biochemical parameter suggest cytokine storm and patient can develop multiorgan failure.[4]

The relatively high infectivity, rapid progression of lung involvement, and absence of definite effective treatment

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all contribute to a need to design effective measures for the management of COVID-19 based on the disease pathogenesis. Although many types of research and studies have contributed to the understanding of the disease and various empirical therapeutic options have been introduced on several operational methods, including the existing and new generation of antivirals and traditional medicine. An effective therapeutic option has not been achieved for severe COVID-19 cases.[5-8]

Corticosteroids have been used previously in respiratory illnesses such as asthma, COPD, severe bacterial pneumonia, and acute respiratory distress syndrome. The use of corticosteroids on COVID-19 disease is still controversial.[9] Some studies have shown a good response to steroids as they reduce inflammation,[10,11] However corticosteroids suppress the patients immunity making him more prone to superadded infection.[10,12] Recently, the recovery trial in the U.K. showed dexamethasone (DEXA) (corticosteroid) to be the only drug able to reduce mortality in severe COVID-19 disease.[13]

However, there is a paucity of literature on the use of methylprednisolone (MTP) in COVID-19. Hence, this study has been under taken to compare the role of DEXA with MTP in patients of COVID-19.

Aims and objectives

To compare the efficacy and outcome of MTP and DEXA in moderate to severe COVID-19 disease.

MATERIALS AND METHODS

The current study is a prospective study involving 140 patients diagnosed with moderate to severe COVID-19 disease admitted in Kaily Hospital Mahirshi Vashisth Autonomous State Medical College, Basti, U.P. from 15 April to 15 June 2021.

Inclusion criteria

- Age: 18–75 years.
- COVID-19 RT-PCR positive.
- Moderate-to-severe COVID-19 cases according to definition.
- Patients having oxygen saturation <93% on room air, regardless of chest X-ray infiltrates.
- Patients given informed consent.

Exclusion criteria

- Pregnant or lactating females.
- Immunocompromised conditions such as HIV or long-term use of immunosuppressant for any chronic illness.

Study

We enrolled 140 patients admitted in Kaily hospital Mahirshi Vashisth Autonomous state Medical College, Basti U.P. who fulfilled the inclusion criteria and signed informed consent.

After admission, Baseline oxygen saturation and clinical findings were noted. Chest X-ray was done on admission and laboratory tests were performed such as haemogram, liver function test, kidney function test, C-reactive protein (CRP), Serum ferritin (S. ferritin), lactate dehydrogenase (LDH), and D-dimer. Low molecular weight heparin (Enoxaparin) was prescribed to all patients to prevent thromboembolism and antibiotics also during their hospital stay.

Patients were divided into two groups. Group A (n=70) and Group B (n=70). Group A received intravenous methylprednisolone (MTP) 2.0 mg/kg bodyweight for 3 days followed by 1.0 mg/kg for 3 days in the divided dose and Group B received DEXA 8 mg/day intravenously daily in divided dose up to 10 days. Oxygen saturation was recorded daily and laboratory investigations such as CRP, LDH, S. ferritin, and repeat chest X-ray were performed after 5 days and also after 10 days. Patients were given oxygen by nasal cannula, face mask, and non-rebreathing mask. Patients were shifted to ICU if clinical condition deteriorated and/or mechanical ventilation was needed.

We compared outcomes on the basis of clinical, radiological, biochemical parameters and mortality of patients on day 0 that is admission day, 5th and 10th days between both drugs.

Data were analyzed using SPSS 26.0 mean and standard deviation was computed for quantitative variables whereas frequency and percentage were calculated for other category variables.

RESULTS

A total of 140 patients of COVID-19 having moderate to severe COVID-19 disease and admitted to Kaily Hospital, MVASMC Basti fulfilling inclusion criteria were recruited in the study. Out of 140, 70 patients received MTP (Group-A) and the other 70 patients received DEXA (Group-B).

The mean age in MTP group was found to be 45.5 years and 45.34 years in DEXA group (Table 1).

Both groups were compared for underlying diseases such as diabetes, hypertension, COPD, renal disease, and hypothyroidism. There was no statistically significant

difference between both groups but hypertension was found in 16 patients in group A while in group B hypertension was found in 26 patients (P<0.05).

On completion of 10 days of treatment with parental corticosteroids, the biochemical markers of severity improved significantly in MTP as well as DEXA group (Table 2).

Patients were evaluated on day 0, 5, and 10. There was a significant clinical improvement in the MTP group as compared to the DEXA group (92.85% vs. 81.42%, P<0.05).

Radiological improvement was statistically significant in the MTP group when compared to the DEXA group (82.8% vs. 68.5%, P<0.05).

Transfer to intensive care unit and ventilator requirement was lower in the group that received MTP (5.71% vs. 14.28%) and (2.85% vs. 8.57%), respectively (Table 3).

Hyperglycemia was more frequent in the DEXA group (18.57%) as compared to the MTP group (7.14%) (P<0.05). In terms of mortality, group B reported 13 cases (18.5%) while in group A five patients died (7.14%). The difference was statistically significant (P<0.05).

Z test for proportion (one-tailed) is carried out to see if there any proportion difference between two drug groups for variables under study. P-value (for one-tailed alternative) showing there is significantly more clinically improved and radiologically improved patients are in MTP group and also for hyperglycemia and mortality, there is significantly lesser proportion of patients in MTP group.

Table 1: Socio-demographic and clinical characteristics of hospitalized patients with COVID-19 pneumonia, according to treatment group

S. No.	Variable	MTP (Group-A) n=70	DEXA (Group-B) n=70	Total n=140	P-value
1.	Age (years)	Mean age 45.50	Mean age 45.34		0.949
2.	Sex				
	Male	46 (65.71%)	50 (71.42%)	96 (68.57%)	0.466
	Female	24 (34.28%)	20 (28.57%)	44 (31.42%)	
3.	Diabetes mellitus	16 (22.85%)	19 (27.14%)	35 (25.0%)	0.612
4.	CKD	06 (8.57%)	07 (10.0%)	13 (9.28%)	0.781
5.	Hypertension	16 (22.85%)	26 (37.14%)	42 (30.0%)	0.048
6.	COPD	09 (12.85%)	06 (8.57%)	15 (10.71%)	0.438
7.	Hypothyroidism	06 (8.57%)	04 (5.71%)	10 (7.14%)	0.527
8.	Heart disease	03 (4.28%)	03 (4.28%)	06 (4.28%)	1.0
9.	Obesity	07 (10.0%)	06 (8.57%)	13 (9.28%)	0.781
10.	Malignancy	02 (2.85%)	01 (1.42%)	03 (2.14%)	0.563

CKD: Chronic kidney disease, MTP: Methylprednisolone, DEXA: Dexamethasone, COPD: Chronic obstructive pulmonary disease. T-test is performed to see if there any mean age difference between MTP and DEXA group, *P* value is coming out to be greater than 0.05, means there is no mean age difference. Chi-square test is carried out to see if there any association between two groups of drug for variable under consideration. There is a significant association between hypertension and two groups of drug. For other variable, *P* value is coming out to be more than 0.05, showing there is no significant association

Table 2: Comparison of intervention between two groups

Medicine or treatment	Variable	Mean+SD MTP (Group-A)	Mean+SD DEXA (Group-B)	P-value
On day 0	SPO_2	89.91±2.05	90±1.91	0.799
	CRP	112.49±46.91	110.62±48.37	0.816
	S.Ferritin	186.85±167.96	190.20±94.40	0.885
	LDH	315.63±184.36	318.40±131.23	0.9187
Day 5	SPO_2	91.90±1.05	91.00±2.70	0.013
	CRP	58.62±39.001	75.52±50.014	0.032
	S.Ferritin	134.14±123.135	142.95±101.215	0.655
	LDH	272.29±151.83	282.40±163.16	0.713
Day 10	SPO_2	94.48±81	93.60±5.411	0.204
	CRP	28.00±7.605	31.30±8.934	0.032
	S. Ferritin	88.56±42.82	93.54±47.14	0.544
	LDH	188.49±47.22	190.28±39.119	0.823
		Greenhouse- Geisser (P=0.00)	Greenhouse- Geisser (P=0.00)	

CRP: C-reactive protein; S. Ferritin: Serum ferritin; LDH: Lactate Dehydrogenase. Greenhouse-Geisser (P-value) showing there is a significant difference over time within a group for all variables under study. T-test is carried out to see if there any mean difference for variables under consideration for drug A and B. At 0 day, there is no significant difference between drug group A and B for all variables. (P>0.05) At day 5, S. ferritin and LDH showing no difference in drug group A and B. While in SPO_2 and CRP there is significant mean difference for the drug. At day 10, only CRP is showing significant mean difference for the two drug group

Table 3: Clinical outcome of hospitalized patients with COVID-19 pneumonia according to the treatment group

Variables	MTP (Group-A) n=70	DEXA (Group-B) n=70	Total patients n=140	P-value
Clinically improved	65 (92.85%)	57 (81.42%)	122 (87.14%)	0.0433
Radiologically improved	58 (82.85%)	48 (68.57%)	106 (75.71%)	0.0487
Hyperglycemia	05 (7.14%)	13 (18.57%)	18 (12.85%)	0.046
ICU transfer	04 (5.71%)	10 (14.28%)	14 (10.0%)	0.090
Ventilator need	02 (2.85%)	06 (8.57%)	08 (5.71%)	0.145
Hyperglycemic coma/DKA	0.0 (0.0%)	0.0 (0.0%)	0.0 (0.0%)	0
Superadded infection	0.0 (0.0%)	0.0 (0.0%)	0.0 (0.0%)	0
Mortality	05 (7.14%)	13 (18.57%)	18 (12.85%)	0.0433

CKD: Chronic kidney disease, MTP: Methylprednisolone, DEXA: Dexamethasone

For other variables, the result is coming not out to be significant.

DISCUSSION

COVID-19 disease is caused by SARS-CoV-2 has emerged as a major threat globally. The novelty of disease and its undesirably high morbidity and mortality have lead physicians to explore new dimensions of treatment.

ARDS and cytokine release syndrome are dreadful complications of COVID-19, both characterized by increased levels of Tumor necrosis factor Alfa, Interleukin (IL) IB, IL-2, IL-6, IL-8, IL-10, and Interferon-gamma which causes dysregulated auto-inflammatory response, severe tissue inflammation and ultimately death.[14] Due to its anti-inflammatory properties corticosteroids have been used in the treatment of COVID-19. We performed a comprehensive comparison of MTP and DEXA in the treatment of moderate to severe COVID-19 disease.

In the current study, we included 140 patients with moderate to severe COVID-19 disease, they were randomly allocated to two groups, i.e., Group A (MTP group) and group B (DEXA group). Both groups were matched regarding their demographic profile (Table 1).

In MTP group, a more significant decrease in inflammatory response was observed than in DEXA group leading to decrease in CRP, LDH, and S. ferritin. This is consistent to the finding of Pinzón et al.[15]

In a randomized clinical trial performed by Edalatifard et al., the efficacy of intravenous MTP pulse was compared with standard care. In the mentioned study, patients with clinical improvement were higher in MTP group than in the standard care group (94.1% vs. 57.1%). The clinical improvement was noted in terms of increase in oxygen saturation and alleviation of myalgia, chest pain, cough, fever, and gastrointestinal symptoms.[16] These findings were in line with our study. The present study showed a significant clinical improvement (92.8% vs. 81.4%) as well radiological improvement on (82.8% vs. 68.5%) in MTP group when compared with DEXA group (Table 2).

As per study performed by Pinzon et al., patients in DEXA group developed severe ARDS in higher proportion than the MTP group, and transfer to the intensive care unit was less in the MTP group which is related to less clinical deterioration and less progress to critical illness with the administration of high dose of MTP,[15] this was in corroboration with the finding of our study where transfer to ICU was 5.7% in MTP group as compared to 14.2% in DEXA group.

In a retrospective cohort study conducted by Wang et al., in the evaluation of treatment of patients suffering from COVID-19 with low dose of MTP (1–2 mg/kg/day) for 5–7 days had shorter hospital stay and less requirement of mechanical ventilation.[10] These findings were in accordance to the current study (2.8% in MTP group vs. 8.5% in DEXA group).

Treatment of COVID-19 patients with corticosteroids may have some complications like superimposed infection, immunosuppression, and hyperglycemia. Hyperglycemia was more frequent in DEXA group (18.57%) when compared to MTP (7.14%). The hyperglycemia was managed effectively with insulin and none of the patients developed serious complications such as ketoacidosis or hyperosmolar coma. In some studies, it was found that hyperglycemia was more frequent in those who received MTP, managed without substantial complication.[10,16,17]

None of our patients developed superadded bacterial pneumonia as determined by pro-calcitonin levels and serial chest X-ray for new opacities. This could be explained by short period of corticosteroid use (i.e. 5 days). This is similar to the study performed by Fatima et al.[18]

The recovery trial showed significantly less mortality in DEXA group as compared to standard care group.[13] However, the recovery trial did not study the effects of MTP.

Wang et al., conducted a retrospective cohort study of MTP therapy in severe patients of COVID-19 pneumonia and found that there was a significant reduction in morbidity and mortality with MTP.[10]

KO et al., concluded that therapeutic benefits of corticosteroids are not limited to DEXA only. The higher anti-inflammatory potency of MTP had greater mortality benefits in COVID-19 patients requiring mechanical ventilation.[19]

In the present study, there was a significant reduction of mortality in the MTP group as compared to DEXA group (7.14% vs. 18.5%; P<0.05). This is similar to the Edalatifard et al., who showed lower mortality rate in MTP group (5.9% vs. 42.9%, P<0.0001).[16]

Limitations of the study

To the best of our knowledge, this was the first study in eastern Uttar Pradesh, India comparing the efficacy of MTP with DEXA.

However, major limitations of this study are sample size is small and there was no follow-up of patients after discharge.

CONCLUSION

In this study, the severity markers of COVID-19 pneumonia such as CRP, LDH, and S. ferritin are significantly reduced by administration of both MTP as well as DEXA. However, the outcome in the terms of clinical improvement, radiological improvement, reduction in mechanical ventilation requirement, and decrease in mortality was found to be better in MTP group when compared with DEXA group.

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Ferritin – The key model inflammatory marker in diabetic and non-diabetic COVID-19

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ABSTRACT

Background: Diabetics exhibit elevated serum ferritin level when compared to non-diabetic counterpart, indicates impact of its association with coronavirus disease 2019 (COVID-19) infection and disease progression. Ferritin is a key mediator of immune dysregulation through direct immunosuppression contributing to cytokine storm resulting in fatal outcome in COVID-19. **Aims and Objectives:** This study aims to estimate serum ferritin in diabetic (cases) and non-diabetic (controls) COVID-19 patients and its correlation with their diabetic profile (FBS, PPBS, RBS, and HbA1C). **Materials and Methods:** A retrospective case–control study conducted at Rajarajeswari Medical College and Hospital, Bengaluru, for a period of 8 months among diabetic and non-diabetic COVID-19 patients. **Results:** The study population consisted of 957 individuals, out of them, 425 patients were type 2 diabetes mellitus and 532 were non-diabetic COVID-19-positive patients (controls). Diabetic profile parameters (FBS, PPBS, RBS, and HbA1c) and serum ferritin were significantly ($P < 0.05$) high in cases as compared to controls. Among diabetic COVID-19, the glycated hemoglobin and serum ferritin showed a significantly positive correlation ($r = 0.55$) with serum ferritin (mean = 648.98 ± 320.48). **Conclusion:** Hyperferritinemia is more prevalent in diabetic COVID-19 individuals. Serum ferritin can be considered as a valuable biomarker to screen the diabetic and non-diabetic for the presence of hyperinflammation and to predict severity of COVID-19 infection so that it will help the clinician for proper management.

Key words: Type 2 diabetes mellitus; $HbA1_c$; Serum ferritin; Severe acute respiratory syndrome coronavirus-2

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INTRODUCTION

In December 2019, a sequence of pneumonia cases of unknown cause was reported in Wuhan, Hubei, China. Later on, the novel coronavirus was isolated from respiratory tract samples named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The new virus swiftly unfolds globally ensuing in a pandemic by the WHO on March 11, 2020.[1]

The disease due to SARS-CoV-2 is referred as coronavirus disease 2019 (COVID-19) tiers from moderate acute respiratory illness to extreme pneumonia with respiratory failure, acute respiratory distress syndrome, and septic shock.[2] As per the WHO, the COVID-19 virus infects people of all ages. Older adults and those with underlying medical comorbidities, such as hypertension, diabetes, chronic lung disease, cardiovascular disease, chronic kidney disease, and cancer are at higher risk of severity of illness.[3,4]

Diabetes is a metabolic disorder characterized by hyperglycemia from defects in insulin secretion, insulin action, or both.[5] People with type 2 diabetes mellitus develop characteristic microvascular and macrovascular complications such as retinopathy, nephropathy, and neuropathy. Complications due to diabetes are a major cause of disability which reduces quality of life and leads to death. Compared to non-diabetic, diabetics have an immunocomprised status, which tends to reduce their resistance and make them more vulnerable to corona like infections as well as consequent complications.[6]

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The prevalence of diabetes in patients with COVID-19 depends on duration and characteristics of study population. In a multicenter study with 1099 patients hospitalized with COVID-19 illness in China, the overall prevalence of diabetes was 7.4%.[7] In a meta-analysis of seven studies including 1576 patients from China, diabetes was the second most common comorbidity following hypertension and was present in 9.7% of patients.[8] In another meta-analysis of 21 studies mainly from China, hypertension and diabetes were the foremost prevalent comorbidities present in 15.6% and 7.7%, respectively, among 47,344 patients with COVID-19.[9]

Studies suggest that the low-grade chronic inflammation along with the hypercoagulable state in diabetes may promote the cytokine storm, a complication of severe COVID-19 which is characterized by excessive production of inflammatory cytokines (IL-6, IL-10, and TNF-α).[10] Ferritin is a key mediator of immune dysregulation through direct immunosuppression contributing to cytokine storm resulting in fatal outcome in COVID-19.[11] Diabetic exhibits elevated serum ferritin level when compared to non-diabetic counterpart indicates impact of its association with infection and disease progression.[12]

Approximately 5.1 million people aged between 20 and 79 years died from diabetes accounting for 8.4% of global all-cause mortality in this age group.[13] In India, 65.1 million in the age group of 20–79 have diabetes (8.56%) and expected to rise to 109 million by the year 2035.[14] Diabetes is associated with increased mortality rate in patients with COVID-19 and is considered as a major risk factor for COVID-19 infection. As per the study done by American Diabetic Association among the people with diabetes COVID-19, the mortality rate was 7.3%. Two other conditions that are common in those with diabetes were also associated with higher mortality rates: 10.5% for cardiovascular disease and 6.0% for hypertension. Diabetics experience higher rates of mortality and are less likely to be discharged when compared with non-diabetic patients.[15] Because mortality rates were not stratified by age, it is not clear how much of the excess risk in people with these conditions was independently related to age. The symptoms of COVID-19, including fever, shortness of breath, and cough, were mostly reported in diabetic patients than in non-diabetic patients, while chest pain, sore throat, and decreased sense of smell and taste were more common in non-diabetic COVID-19 patients. In a study conducted in China, fever, dry cough, and fatigue were the most common symptoms in diabetic COVID-19 patients[16] and another study showed cough and fever as the most common symptoms in these patients.[17]

To the best of our knowledge, there is a paucity of literature, especially from India showing direct evidence of relation between diabetes mellitus and ferritin in COVID-19. This study is the first of its kind in South Indian population with large sample size. This research was designed to enlighten this path and to compare serum ferritin in diabetic (cases) and non-diabetic (controls) COVID-19 patients and the association of elevated serum ferritin level with diabetic profile (glycated hemoglobin, FBS, PPBS, and RBS) in type 2 diabetes mellitus.

Aims and objectives

The aims of the study were as follows:

1. To estimate and correlate serum ferritin in diabetic (cases) and non-diabetic (controls) COVID-19 patients
2. To correlate the diabetic profile (FBS, PPBS, RBS, and HbA1C) with ferritin in diabetic (cases) and non-diabetic (controls) COVID-19 patients.

MATERIALS AND METHODS

Study design

The study was pre-approved by the Institutional Ethics Committee for the final permission. This case–control retrospective study was conducted at Rajarajeswari Medical College and Hospital, Bengaluru, for a period of 8 months (May 2020–December 2020). Type 2 diabetes mellitus and non-diabetic patients, irrespective of the gender, in the age group of 18–75 years, admitted at Rajarajeswari Medical College and Hospital, diagnosed as COVID-19 positive following COVID-19 RT-PCR test was enrolled as cases and controls, respectively.

Inclusion criteria

Type 2 diabetes mellitus patients, irrespective of diabetic control, who tested positive for COVID-19, with or without diabetic complications and with or without antidiabetic treatment, were the study cases.

Exclusion criteria

(1) Type 1 diabetes mellitus and (2) both cases and controls with a history of diseases which alter the serum ferritin levels such as hemochromatosis, chronic alcoholics, chronic inflammatory conditions like SLE/rheumatoid arthritis, hepatitis, history of repeated blood transfusions, iron deficiency anemia, hypothyroidism, and chronic kidney disease were excluded from the study.

Sample collection and processing

After obtaining informed consent from study subjects, under all aseptic precautions, 2 ml of venous blood sample was collected in fluoride EDTA tube in fasting and postprandial state and 5 ml in red capped and Lavender capped collection tubes for sr. ferritin and for HbA1c estimation, respectively. Estimation of FBS, PPBS, RBS, HbA1c, and serum ferritin was carried out.

Table 1: Correlation between serum ferritin and different HbA1c ranges among diabetic COVID-19 cases (n=425)

HbA1C % range	n (%)	Mean±SD HbA1C%	Serum ferritin (ng/mL)	Pearson's correlation r value	P-value
5–5.9	6 (1.4)	5.76±0.19	371±398.66	-0.41	0.19
6–7.5	214 (50.4)	6.72±0.44	497.32±310.81	0.57	0.00
7.51–9	116 (27.3)	8.1±0.44	761.91±201.21	0.256	0.004
9.01–10.5	39 (9.2)	9.5±0.38	843±210.10	0.25	0.11
>10.5	50 (11.8)	11.55±0.65	918.19±281.77	0.03	0.79

Table 2: Baseline characteristics of the entire study population

Variable	Diabetic COVID-19 cases	Non-diabetic COVID-19 controls	t-value	*P*-value
Age	52.89±14.14	43.80±16.50	9.01	0.000
RBS	180.64±48.11	104.63±18.63	39.67	0.000
FBS	291.86±91.54	82.61±8.90	46.01	0.000
PPBS	281.38±100.64	126.26±10.69	41.37	0.000
Hba1c	7.92±1.67	4.50±0.31	47.99	0.000
Serum ferritin	648.98±320.48	204.39±248.18	24.18	0.000

FBS, PPBS, and RBS were estimated by GOD-POD enzymatic method in fully automated Beckman Coulter Autoanalyzer. HbA1c was tested by BIORAD D10 system which is based on the principle of high-performance liquid chromatography. Serum ferritin was assayed by electrochemiluminescence method. Diabetic patients tested for HbA1C were arranged into five groups, as listed in Table 1. Reference range of FBS, PPBS, and RBS was 70–100 mg/dl, <140 mg/dl, and 70–140 mg/dl, respectively. Reference range of HbA1c was 5–6.5%, and serum ferritin 24–336 ng/ml in adult males and 11–306 ng/ml in adult females were considered.

Statistical analysis

Data were entered into MS Excel sheet and analyzed using SPSS version 20.0. The descriptive statistics, that is, all qualitative variables were presented as frequency and percentages. All quantitative variables used to correlate the serum ferritin levels between diabetic and non-diabetic groups were presented as mean and standard deviation test. Pearson's correlation test was applied to check the correlation between serum ferritin with parameters such as FBS, PPBS, and RBS among both groups. p <0.05 was considered to be statistically significant. Pearson's r varies between +1 and –1, where +1 is a perfect positive correlation and –1 is a perfect negative correlation. Zero means that there is no linear correlation at all.

RESULTS

A total of 957 subjects were enrolled for the study consisting of 425 cases and 532 controls.

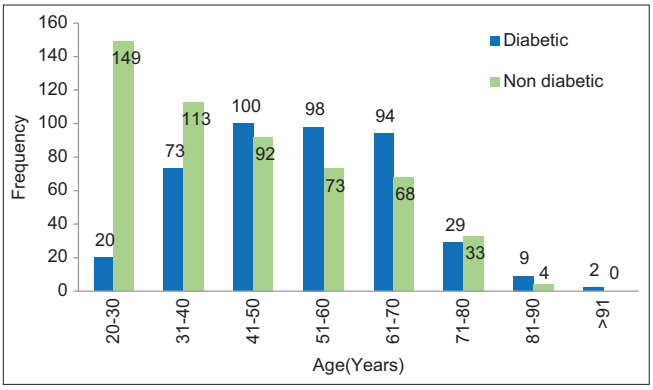

Figure 1: Age-wise distribution of entire study population

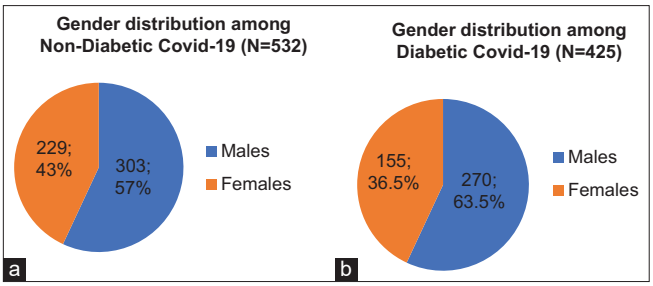

Figure 2: (a and b) Gender distribution of diabetic coronavirus disease 2019 (COVID-19) cases and non-diabetic COVID-19 controls

The mean age of the study participants among diabetic cases was 52.89±14 years which is significantly higher when compared to the non-diabetic COVID-19 control group 43.80±16.50 years (Figure 1).

Majority of the study subjects were males in both cases (57%) and controls (63.5%) (Figure 2).

Baseline characteristics of the entire study population are depicted in Table 2. The mean levels of diabetic profile parameters (FBS, PPBS, RBS, and HbA1c) were significantly higher (P<0.05) in diabetic COVID-19 cases compared to the mean values of non-diabetic COVID-19 controls. On comparison of serum ferritin levels between diabetics and non-diabetic COVID-19, it was found that mean serum ferritin level was significantly higher in cases compared to controls and the difference was statistically significant (P<0.05).

On comparison of gender-wise difference in the serum ferritin among both groups, it was observed that the mean

Table 3: Gender-wise distribution of serum ferritin among diabetic COVID-19 cases and non-diabetic COVID-19 cases

Variable	Serum ferritin		t-value	P-value
	Males	Females		
Diabetic COVID-19 cases	679.11±325.20	596.48±303.96	7.92	<0.0001
Non-diabetic COVID-19 controls	274.58±273.19	111.53±170.08	2.57	0.005

Table 4: Correlation between serum ferritin and HbA1c levels in diabetic COVID-19 cases and non-diabetic COVID-19 controls

Variables	Mean	Standard deviation	Pearson's correlation r value	P-value
Diabetic COVID-19 cases				
Serum ferritin	648.98	320.48	0.55	0.00
HbA1C	7.92	1.67		
Non-diabetic COVID-19 controls				
Serum ferritin	207.83	249.39	0.068	0.11
HbA1C	4.50	0.31		

serum ferritin among males was higher than females in both diabetic and non-diabetic COVID-19 groups and this gender-wise difference in the mean values of serum ferritin was found to be statistically significant in both case and and control groups (P<0.05) (Table 3).

The correlation between glycated hemoglobin and serum ferritin was done by Pearson's correlation test and it showed a statistically significant (P≤0.05) positive correlation (r=0.55) in diabetic Covid-19 cases (Table 4) and (Figure 3). The correlation between serum ferritin and HbA1c amongst controls showed weak positive correlation which was not statistically significant (P=0.11) (Table 4) (Figure 4).

Mean±SD value of serum ferritin level in different HbA1c range was measured. Mean ferritin of all the groups of glycated hemoglobin was calculated and highest mean ferritin was seen in the poorly controlled diabetic group with HbA1c >10.5% with mean ferritin value 918.19±281.77 ng/mL (Table 1).

Mean serum Ferritin (793±232 ng/mL) was reported to be high among the poorly controlled (HbA1c>7.1) compared to well controlled (HbA1c<7) diabetic Covid-19 cases (403 ±300 ng/mL) with statistically significant positive correlation (Table 5) and (Figures 5 and 6). It is also observed that the serum ferritin value increases with increase in HbA1c level in diabetic Covid-19 cases with statistically significant positive correlation (Table 1).

Correlation analysis of serum ferritin with diabetic profile parameters in diabetic COVID-19 cases revealed that there was a moderate positive correlation between serum ferritin and FBS (r=+0.55), PPBS (r=+0.50), and RBS (r=+0.46) which was found to be statistically significant (p<0.05), however, the correlation between age (r=0.09) and serum ferritin was not statistically significant (Table 6).

Among non-diabetic COVID-19 controls, there was a statistically significant (P<0.05) positive weak linear correlation between serum ferritin and age (r=0.166), PPBS (r=0.107), and RBS (r=0.20). The weak linear positive correlation between FBS (r=0.068) and serum ferritin was not statistically significant (P>0.05) (Table 7).

DISCUSSION

COVID-19 respiratory infection being very contagious and is prevalent in diabetics who are prone for infections easily. COVID-19 patients rapidly progress to metabolic acidosis, coagulopathy, acute respiratory failure, and septic shock. Early identification of risk factors for worsening of the disease is very vital in the treatment and prognosis of the COVID-19 disease. Diabetes and its associated factors such as increased age, comorbidities, poor diabetic control, and hyperferritinemia in the affected COVID-19 individuals will add to the problem. Qin et al., in their cohort, observed at least one underlying disorder (hypertension, diabetes, and chronic obstructive pulmonary disease) in severe cases compared to mild cases.[18]

Studies show that in severe COVID-19 infection, there will be not only pulmonary but also there will be systemic inflammatory response with raised serum levels of several inflammatory markers including serum ferritin which ultimately result in cytokine storm. Diabetics have elevated serum levels of ferritin,[12,19] so they are more likely to encounter severe complications during COVID-19 infection as viral infections can also increase inflammation in people with diabetes.

Innumerable studies are carried out during this pandemic to understand the various aspects of this deadly disease. Due to high mortality and morbidity of COVID-19 infection, search of various and better hematological and biochemical parameter was carried out to assess the severity

Table 5: Correlation between serum ferritin and HbA1c among well controlled and poorly controlled diabetic COVID-19 cases (n=425)

HbA1C % range	n (%)	Mean±SD HbA1C%	Serum ferritin (ng/mL)	Pearson's correlation r value	P-value
Well-controlled (<7%) diabetic COVID-19 cases	157 (36)	6.46±0.32	402.98±299.48	0.297	0.0015
Poorly controlled (>7.1) diabetic COVID-19 cases	268 (63)	8.77±1.55	793.08±231.89	0.330	<0.0001

Table 6: Pearson correlation of serum ferritin with age, FBS, PPBS, and RBS parameters among diabetic COVID-19 cases

Parameter	Pearson's correlation r value	P-value	Interpretation
Age versus serum ferritin	0.09	0.06	Not significant
FBS versus serum ferritin	0.55	0.00	Significant
PPBS versus serum ferritin	0.50	0.00	Significant
RBS versus serum ferritin	0.46	0.00	Significant

Table 7: Pearson correlation of serum ferritin with age, FBS, PPBS, and RBS in non-diabetic COVID-19 controls

Parameter	Pearson correlation r value	P-value	Interpretation
Age versus S. ferritin	0.166	0.00	Significant
FBS versus S. ferritin	0.068	0.11	Not Significant
PPBS versus S. ferritin	0.107	0.01	Significant
RBS versus S. ferritin	0.200	0.00	Significant

and prognosis of the disease. This study will give an insight into the role of inflammatory marker serum ferritin and diabetic profile parameters in COVID-19 infection in diabetics and non-diabetics.

In this study, males were more affected by COVID-19 infection (cases 57% and controls 63.5%). In other similar studies, male preponderance was observed. Fan et al., observed male preponderance in their study.[20]

In the present study, COVID-19 infection was seen to be more prevalent in the age group of 30–70 years in diabetic COVID-19 cases and 20–70 years in non-diabetic COVID-19 controls. The mean age of the study participants was significantly (P<0.05) high among diabetic cases (52.89±14 years) compared to non-diabetic COVID-19 control group (43.80±16.50 years). Wu et al., and Qin et al., in their study concluded that increasing age with comorbidities is the risk factor for contracting acute respiratory distress syndrome and death due to decreased immune response.[18,21] Thus, the age factor will be the additional risk factor for the bad prognosis in diabetic COVID-19 individuals. Zhou et al.,[22] observed that old age was associated with more ICU admissions. Bozkurt et al., also observed high number of elderly diabetic individuals amongst severe COVID-19 patients.[23]

In this study, the correlation between age (r=0.09) and serum ferritin was not statistically significant in cases. However, among non-diabetic controls, there was statistically significant (P<0.05) positive weak linear correlation observed between serum ferritin and age (r=0.166).

In the present study, serum levels of diabetic profile parameters (FBS, PPBS, RBS, and HbA1c) were significantly (P<0.05) high in cases when compared to controls. Similar result was found by Rawat et al.[24] In the present study, statistically significant high levels of HbA1c were observed in cases compared to controls. Liu et al., observed patients with high HbA1c (≥6.5%) or fasting glucose level (≥126 mg/dl) on admission had increased risk of mortality.[25]

Statistically significant increased levels of serum ferritin level were observed in this study as the HbA1c level increased in cases. Statistically significant high levels of serum ferritin were also seen in poorly controlled diabetic COVID-19 cases compared to well-controlled diabetic COVID-19 cases. Correlation analysis among diabetic COVID-19 cases and non-diabetic COVID-19 controls indicates that serum ferritin level increases as the glucose level increases in the body.

Literature search regarding glucose metabolism in COVID-19 individuals shows that hyperglycemia promotes SARS-CoV-2 replication in human monocytes, resulting in increased viral proliferation Codo et al.[26] Thus, hyperglycemia is an independent risk factor for frequent occurrence of COVID-19 infection in diabetic individuals. In diabetic MERS-CoV-infected animal (mice) studies, extensive lung pathology was observed due to dysregulated immune response, Kulcsar et al.[27] Lim et al.,[28] also observed severe lung involvement in COVID-19 patients with poor glycemic control. Hence, hyperglycemia may be the cause

for severe COVID-19 infection and increased need of hospitalization, ICU care, and increased mortality and morbidity. SARS-CoV-2 replication also produces more mitochondrial reactive oxygen species and activation of hypoxia-inducible factor 1α.[29] Therefore, patients with diabetes mellitus typically fall into higher categories of SARS-CoV-2 infection severity than those without[21,30] and poor glycemic control predicts an increased need for medications and hospitalizations, and increased mortality.[31]

Patients with iron overload have high ferritin levels. Increased accumulation of iron affects insulin synthesis and secretion in the pancreas and interferes with the insulin extracting capacity of the liver. Conversely, insulin stimulates cellular iron uptake through increased transferrin receptor externalization. Excessive iron accumulation can induce organic damage that leads to diabetes.[32-34] Thus, insulin and iron can mutually potentiate their effects, leading, after a vicious cycle, to insulin resistance and diabetes.[35-37]

Ferritin is an inflammatory marker located in heart, liver, kidney, spleen, and intestinal mucosal cells but it is unclear whether serum ferritin reflects or causes inflammation, or whether it is involved in an inflammatory cycle. Kell et al., found that serum ferritin arises from damaged cells and is thus a marker of cellular damage.[38]

Ferritin has no circadian rhythm and completely taken up by liver. Ferritin has more expression time than other inflammatory markers such as IL-6 and IL-10, hence, it is better predictor of disease progression.[39]

Results of this study showed were significantly higher levels of serum ferritin in the cases compared to controls ($P<0.05$). Serum levels of ferritin, an iron storing protein increases during COVID-19 infection. The inflammatory cytokines produced during cytokine storm stimulate the hepatocytes, macrophages, and Kupffer cells to secrete ferritin.[39-41]

The alterations of the immune regulation appear to be the cause for advancement of disease from an asymptomatic or mild infection to a severe disease with poor prognosis. Ferritin, in particular under severe hyperferritinemia, is a key mediator of immune dysregulation through direct immune suppressive and pro-inflammatory effects, leading to cytokine storm.[42] Several studies suggest that increased levels of serum ferritin and other inflammatory markers in severe and critical patients as compared to mild and moderate patients.[18,43-45] In a retrospective cohort study from Wuhan, China, Terpo et al., reported increased ferritin and LDH as risk factors for acute respiratory distress syndrome, ICU support, and mortality.[46]

Bozkurt et al.,[23] observed high levels of serum ferritin in severe COVID-19 patients compared to mild COVID-19 patients. A meta-analysis conducted by Cheng et al.,47 concluded that hyperferritinemia predicts poor prognosis and worsening of COVID-19.

The previous studies interpret that hyperglycemia and hyperferritinemia individually are independent risk factor for the increased severity of COVID-19 infection. Presence of both the risk factors together in a COVID-19 individual worsens the situation. This will alarm the addition of serum ferritin estimation not only in diabetic COVID-19 individuals but also in non-diabetic COVID-19 individuals.

To summarize, the COVID-19 caused by the SARS-CoV-2 is characterized by a human-to-human transmission. Hyperglycemia promotes viral replication and prone for viral infection. Increased serum ferritin level following COVID-19 infection adds on to the problem. Vulnerability of diabetics for infection, associated hyperferritinemia makes diabetes, the major risk factor for fatal outcome in COVID-19. Hyperferritinemia leads to multiorgan

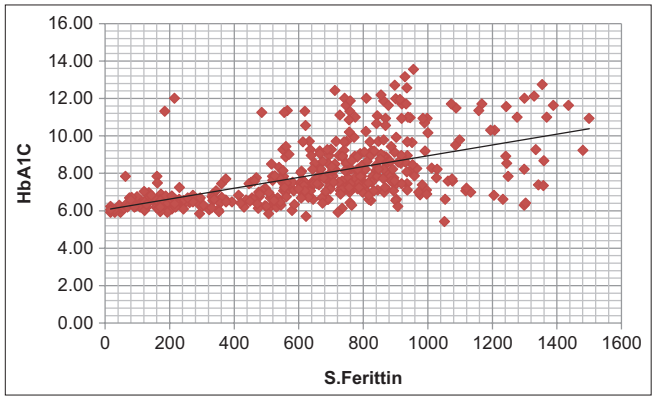

Figure 3: Scatter diagram showing correlation between serum ferritin and glycated hemoglobin in diabetic COVID-19 cases

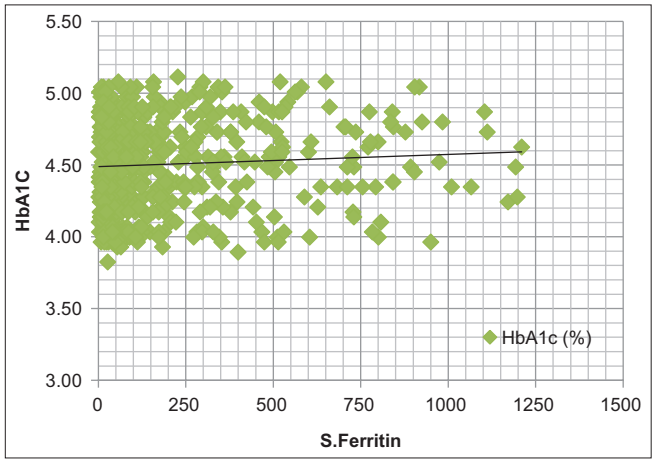

Figure 4: Scatter diagram showing correlation between serum ferritin and glycated hemoglobin among non-diabetic COVID-19 controls

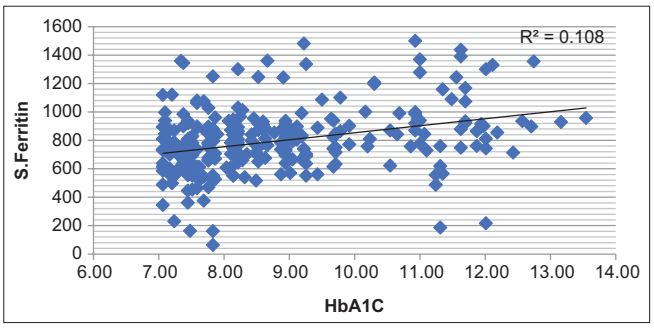

Figure 5: Correlation between serum Ferritin and HbA1c among well controlled Diabetic cases (N=425)

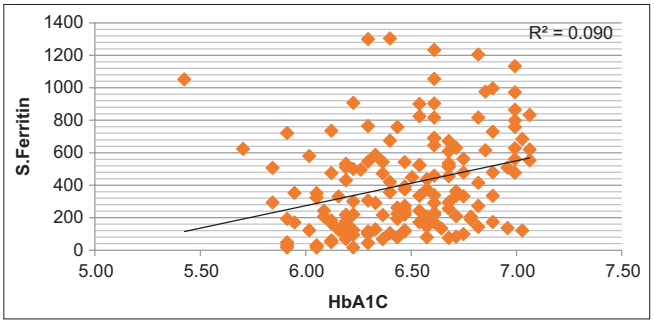

Figure 6: Correlation between serum ferritin and HbA1c among poorly controlled diabetic cases (n=425)

damage and increases the severity of infection. Increased age with decreased immune regulation is an additional risk factor for corona infection. These multiple factors together increase mortality and morbidity of COVID-19 infection. Serum ferritin can be considered as a valuable biomarker to screen the diabetic and non-diabetic for the presence of hyperinflammation and to predict severity of COVID-19 infection so that it will help to prevent end-organ damage.

Limitations of the study

COVID-19 patients were not categorized in to mild, moderate, and severe. Other inflammatory markers were also not measured.

CONCLUSION

Hyperferritinemia is prevalent in diabetic COVID-19 individuals. Hence, the estimation of inflammatory biomarker serum ferritin may be considered for the early prediction of severity of COVID-19 infection, guiding the clinician for proper management of COVID-19 patients and helping in reducing the disease morbidity and mortality.

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Occurrence of COVID-19 in Kolkata slums during second surge

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ABSTRACT

Background: The clobber of COVID-19 brought a coup-de-grace to humanity in this modern era. New-norms of COVID-19 prevention although appear promising yet often adjunct with non-congruent compliance. The WHO has advocated house-to-house case-linked study to acquire facts on epidemiological and transmissibility traits of COVID-19 in low-income communities. Kolkata experienced the first wave of COVID-19 till November 20, expected second splatter in March 21. **Aims and Objectives:** Thinking through a probable upswing of COVID-19 in Kolkata, it was felt prudent to study the occurrence of COVID-19 among residents of two different slums inter-alia study allied factors, if any. **Materials and Methods:** The study was carried out in two different slums having 395 and 428 members, respectively, in South Kolkata from March 21 to August 21. Sanction was obtained from administrative authority as well from each individual. Questionnaire containing personal details, awareness, and observance of personal protective measures (PPM) on COVID-19 were sent to members through e-mode; those demurred, contacted in-person under new-norm. Data assembled was coded, tabulated and analyzed. Details of COVID-19 (RT-PCR + ve) cases confirmed by Government/private hospitals were incorporated as and when surfaced. **Results:** Communities studied had comparable socio-demographic attributes including education, employment, and economic stand. About 93% of subjects from each slum knew most of the facets of PPM and stated practiced the same. Occurrence rates of COVID-19 were 15.2 and 16.2 per 1000 people of respective communities during study tenure. Majority of indisposed were smoker male (92%) from the lowest SES (53.8%), educated to primary/middle school (46%), and worked as vegetable seller (53.8%). All afflicted stated followed PPM except social distancing (77%) and sanitizer use (53.8%). All affected were smokers/quid-users and shared tobacco sticks/hand-smothered quid for mutual use regularly. The study unveiled unequivocal heterogeneity of COVID-19 transmission in Kolkata slums because of certain unattended socio-graphics besides optimistic reflective of PPM awareness/observance. PPM proffers protection no doubt but its effective role necessitates consistent conformity in the background of certain contextual considerations. **Conclusion:** Further research in urban slums is contemplated to enhance the present effort to extricate facts that may lend a hand in COVID-19 prevention tomorrow.

Key words: COVID-19; PPM; Second surge; Social distancing

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INTRODUCTION

The carnage of cankerous COVID 19 has been unprecedented and unheard-of in the history of mankind. Around the world, 216 million have been infected causing 4.45 million fatalities by August 21 with the US leading having estimated 38.5 million cases and India relented for 32.7 million affected.[1] Low-middle-income countries hold the majority of confirmed cases of COVID-19 with India housing the second-highest number of cases in the world.[2] Preliminary scientific insights about COVID-19 infection originated chiefly from epidemiological data endorsed in the initial stage of cataclysm in China,[3] certain European nations,[4] and North America.[5,6] Sero-surveillance and

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contact tracing were recommended as critical components of effective public health response to COVID-19 to delineate epidemiological kinetics and transmission dynamics within limited resources in high priority countries.[7,8] However house-to-house case-oriented study has also been suggested by WHO to generate information on local, epidemiological and transmissibility characteristics of COVID-19.[9] COVID-19 spreads in communities through daily chores like contact while running errands, eating together, going to work or meeting friends and family. Adherence to strict public control measures is difficult to enforce, often culminating in community-level susceptibility due to uncontrolled actions and behavior of others.[10]

Kolkata is thickly populated with ever-expansive trade and business, shops, and markets in the vicinity of close-nit residential, commercial and shanty settlements with perennial sultry climate perhaps posing strong epidemic threat. Kolkata experienced the first wave of COVID-19 up-till around Nov 2020; has been undergoing ravage of resurgence with escalating cases each day since March 21.[11]

Aims and objectives

Considering the trend, it was decided to determine the occurrence of confirmed COVID-19 cases in two different slums in Kolkata during the strike of the second surge; apropos study associated factors related to such occurrence if any.

MATERIALS AND METHODS

The study was conducted from March 21 to August 21 among the residents of two urban slums located in the Tollygang area, South Kolkata having around 100 and 108 families respectively with about 400 members per colony. Access to these slums was facilitated through local administrative body and sanction was secured from the authorities to carry out the study.

The members were interacted at the outset to explain the intent of the study in March 21 and informed individual consents were collected following necessary COVID-19 precautions. Formal list of all members along with address and mobile no. was made. A relevant questionnaire was arranged after revisiting current literature integrating required modifications due to local factors and issues.

The questionnaire comprised of three segments; the first part contained details of personal attributes besides socio-demographic characteristics with job engagement status of the subjects and the second part had details of understanding of personal protective measures (PPM) against COVID-19 with real-life practices for the same. The third section housed facts of COVID-19 infection among residents, in case such surfaced. Socio-economic status (SES) was ascertained as per current scale.[12] The questionnaire was circulated among few members initially to decide feasibility and modifications if needed.

The final questionnaire was broached to all the members through mobile/electronic media; or else individually (for those not having mobile) in small groups at a time. Any uncertainty in information generated through e-mode was cleared during personal visit. Name, address, and mobile no. of residents were codified for discretion, but the record was preserved to avoid duplication. Name of head of the family and house no. were maintained as primary distinctive identity of the family. New-norm measures such as utilization of mask, hand sanitizer, and social distancing were followed during the interactions. The data acquired was assimilated, tabulated, and statistically validated to infer the outcome.

Communities were monitored for the occurrence of distinct cases of COVID-19 (RT-PCR +ve) affirmed by the Govt/private hospitals/clinics till August 21. Contacts were checked in centres/home for possible secondary attack. Subjects were reinforced again and again the measures for COVID-19 prevention.

RESULTS

Community 1 and 2 resided in South Kolkata around 1.5 km apart. Residences were by and large masonry work with asbestos top single room, while few of them were temporary provisional type. Municipal toilets, public water supply, water hand-pumps, and street lights are around but not enough to render public comfort at large. Drainage system is open, littered with undue drop-offs. Surrounding is messy with irregular trash disposal. State hospital and Govt. dispensaries with medical conveniences are nearby for both the slums. Being located in midst of busy vegetable and grocery market, the locality found overpopulated and congested.

Communities included 395 and 428 members, respectively, with sex ratio of 945.8 and 936.6 females/1000 males correspondingly (Table 1). Majority of the respondents belonged to Hindu religion. Employable (21–60 yr.) constituted 68.3% and 73.4% of the groups, however in reality 240 (60.7%) and 256 (59.8%) were actually engaged sequentially. Under-20 constituted 27 and 23% of the communities; family size recounted as 3.95 and 3.96 respectively.

Majority (38% and 37.6%) members of respective groups were educated to primary level as compared to 33.4–35.5% accomplished middle school (Table 2). 25 and 38 children in respective groups didn't attend school; hence deemed illiterate. Majority of the families (46.3–46.5%) belonged to lower most SES in contrast to 43.3–44.9% were from lower middle SES in the corresponding groups.

Nearly 93% and more members of both the communities knew most of the aspects of COVID-19 infection including benefits of PPM like hand washing with soap and water, use of mask and sanitizer, personal hygiene, social distancing and reporting a doctor/health care facility in case of need (Table 3). Largely these measures were even practiced by the members of both communities in similar proportion matching to their awareness. About 17–18% subject availed first dose of COVID vaccination. Around 14% of the individuals from each community even sought health advices as required.

There were 6 and 7 confirmed COVID-19 cases among the subjects of the communities respectively estimating to an occurrence rate of 15.2 and 16.4/1000 of study population in the tenure of the study (Table 4). Subjects from 40 to 49 years age group were mostly (69.2%) affected; majority (92%) were male and smokers belonging to lowest SES group (53.8%) generally educated up to primary/middle school (46% each) working as vegetable vendors (53.8%). All the affected subjects used mask, washed hands twice a day before meals and observed "no contact greetings" however, only 77% could follow social distancing and 53.8% could apply sanitizer. 84.6% believed contracted the disease at work, however, 23% were admitted in hospital on diagnosis and recovered uneventfully. About 61.5% cases occurred in the month of June 21 and contacts of the sick (21 and 23, respectively) got quarantined at home. Children were not affected. All affected and their contacts were tobacco users and exchanged tobacco sticks/quid for mutual puffs/chews regularly.

DISCUSSION

The age-sex configuration, gender quotient and family size of the communities studied depict mutually comparable features aligning national statistics.[13] 240 (60.7%) and 256 (59.8%) members of the communities were engaged in income generation of which 18% and 20% tendered by fair gender respectively. Men folk mostly worked as vendors, shop runners, hotel attendants, stall workers and security guards; while females worked as domestic help, hospital ayah/sweeper, or extended hand in the work of their spouse. 365(92.1%) and 388 (90.7%) subjects from the communities respectively were literate; that's comparatively higher than documented literacy rate of West Bengal (77%).[14] Around 90% of the subjects hailed from lower-middle and lower-most class of SES. Bare minimum education favoured with small family, trying financial endeavour and meagre social subsistence depicts hardship in human sustenance in Kolkata slums in the face of poor civic facilities.

Table 1: Age, sex, and religion of the subjects

Age group in yrs.	Community 1						Community 2				
	Gender		Religion			Total No. (%)	Gender		Religion		Total No. (%)
	Male	Female	Hindu	Muslim	Other		Male	Female	Hindu	Muslim	
1–10	20	24	40	4	-	44 (11.1)	26	29	50	5	55 (12.8)
11–20	35	27	56	4	2	62 (15.7)	24	20	40	4	44 (10.3)
21–30	48	44	92	-	-	92 (23.2)	58	57	110	5	115 (26.9)
31–40	48	46	90	4	-	94 (23.8)	53	48	93	8	101 (23.6)
41–50	28	26	48	4	2	54 (13.7)	35	32	61	6	67 (15.7)
51–60	14	16	28	2	-	30 (7.6)	16	15	27	4	31 (7.2)
61+	10	9	18	1	-	19 (4.8)	9	6	13	2	15 (3.5)
Total	203 (51.4)	192 (48.6)	372 (94.2)	19 (4.8)	4 (1.0)	395 (100.0)	221 (51.6)	207 (48.4)	394 (92.1)	34 (7.9)	428 (100.0)

Table 2: Education and SES of the subjects

Educational qualification	Community 1 Total (%)	Community 2 Total (%)	Socio-economic status	Community 1 Total (%)	Community 2 Total (%)
Graduate	20 (5.1)	17 (4.0)	Upper	--	--
Secondary	63 (15.9)	58 (13.6)	Upper middle	--	--
Middle School-VIII Std	132 (33.4)	152 (35.5)	Middle	41 (10.4)	37 (8.6)
Primary	150 (38.0)	161 (37.6)	Lower middle	171 (43.3)	192 (44.9)
Illiterate	30 (7.6)	40 (9.3)	Lower	183 (46.3)	199 (46.5)
Total	395 (100.0)	428 (100.0)		395 (100.0)	428 (100.0)

SES: Socio-economic status

Table 3: Awareness and preventive compliance for COVID-19

Current knowledge on COVID-19	Com-1 Aware (No. and %) *n^1-351	Com-2 Aware (No. and %) *n^2-373	P value	Preventive measures	Com-1 Obeyed No. (%) n^1-351	Com-2 Obeyed No. (%) n^2-373	P value
Aware of ongoing COVID-19 spate	326 (92.9)	350 (93.8)	Chi-sq -0.26, NS	Taken COVID vac first dose	61 (17.3)	67 (18.0)	Chi-sq - 0.04, NS
COVID-19 spreads by cough/sneezing	329 (93.7)	352 (94.4)	Chi-sq - 0.13, NS	Following cough sneeze hygiene	329 (93.7)	351 (94.1)	Chi-sq - 0.04, NS
COVID-19 causes death in aged subjects	331 (94.3)	349 (93.6)	Chi-sq - 0.17, NS	Not spitting in public (Govt. instructions)	330 (94.0)	353 (94.6)	Chi-sq - 0.1, NS
Washing hand with soap and water helps	333 (94.9)	354 (94.9)	Chi-sq - 0.98, NS	Washing hand with soap/water twice a day	329 (93.7)	350 (93.8)	Chi-sq - 0.003, NS
Putting mask while outdoor helps	329 (93.7)	352 (94.4)	Chi-sq - 0.13, NS	Using mask while going out	328 (93.4)	352 (94.4)	Chi-sq - 0.26, NS
Social distancing keeps off COVID	330 (94.0)	353 (94.6)	Chi-sq - 0.13, NS	Social distancing in shops and markets	331 (94.3)	352 (94.4)	Chi-sq - 0.001, NS
Daily bath/personal hygiene/clothes help	329 (93.7)	350 (93.8)	Chi-sq -0.003, NS	Daily bathing and maintaining hygiene	351 (100.0)	373 (100.0)	--- -
Alcohol based sanitizer disinfects	329 (93.7)	351 (94.1)	Chi-sq - 0.04, NS	Disinfecting hand with sanitizer	329 (93.7)	350 (93.8)	Chi-sq - 0.003, NS
Hand shake/hugging help spread	330 (94.0)	349 (93.6)	Chi-sq - 0.06, NS	Not shaking hand or hugging anyone	330 (94.0)	349 (93.6)	Chi-sq - 0.06, NS
Report a doctor, if cough, cold and fever	328 (93.4)	352 (94.4)	Chi-sq - 0.26, NS	Reported to doctor as and when required	48 (13.7)	53 (14.2)	Chi-sq - 0.04, NS

*Under-10 children were excluded

Nearly more than 93% from both the communities were familiar with all the facets of COVID-19 aside commonly observed PPM and even practiced the same in similar proportion akin to their awareness. Only 17–18% of subjects availed first dose of COVID vaccination and 14% even sought medical advices as needed. It has been documented in the past that substantial no. of subjects were aware about contagiousness (87.3%), incubation period (57.1%), and symptoms of COVID-19 (cent percent).[15] A recent work reported that washing hands and use of alcohol-based sanitizer (23.3%), cough and sneeze discipline along with the use of mask (19.6%), social distancing (16.1%), and following all PPM collectively (40.2%) forestall COVID-19.[15] Authors ascribed around 95-98% of the educated subjects displayed correct preventive knowledge to avert COVID-19 by following PPM.[16] With 80% of Indians being employed in non-organized sectors, it is possible that observance of PPM to restrain COVID-19 could be a trying exigent no doubt.[17] It has been noted that a large no. of subjects followed PPM adequately by using masks (97.2%), social distancing (95.3%), and hand hygiene (91.2%) that apparently corroborates the findings of present work.[16] Strong governmental initiatives coupled with additive effect of awareness, acceptance, and action by the people made it possible to execute public health policies satisfactorily to counter the spikes of COVID-19 infection.[18]

The occurrence rates of COVID-19 were 15.2 and 16.2/1000 population of the community members during the study period. Taking into account the no. of COVID-19 infection as 1.54 and 21.9 million in West Bengal and India correspondingly for the year 2021 as on 31 Aug 21, the occurrence rates work out to 15.4 and 16.5/1000 population in West Bengal and India respectively.[19,20] Rate of occurrence in present endeavor is comparable to state/national statistics though the latter could possibly be laced with factors like under-reporting, missing statistics due to comorbidity and diagnostic errors in rural-remote areas in the setting of colossal state and national population.

Large contingent of men from 40 to 49 years assemblage (69.2%) mostly belonging to the lowest SES group (53.8%) generally educated up to primary/middle school (46% each) working as vegetable vendors (53.8%) were affected. A study from south India reported that low-income group often suffered higher incidence of COVID-19, implying that COVID-19 may unjustly infect poor class.[21] All indisposed stated used mask, washed hands before meals, and observed distanced-greetings, however, only 77% practiced social distancing and 53.8% used sanitizer.

Tobacco use was generally universal with exchange of tobacco sticks/quid for shared puffs/chews, a sort of habitual customary among vendors/hawkers signifying breach in the protective barrier. Smoking causes goblet cell

Table 4: Socio-demographic characteristics of respondents afflicted with COVID-19

Socio-demographic factors	Community 1	Community 2	Total (%)
Number of subjects affected	6	7	13 (100.0)
Age group			
40–49	4	5	9 (69.2)
50–59	2	2	4 (30.8)
Gender			
Male	5	7	12 (92.3)
Female	1	-	1 (7.7)
SES			
Lower middle	2	4	6 (46.2)
Lower	4	3	7 (53.8)
Education			
Secondary	1	-	1 (7.6)
Middle school	2	4	6 (46.2)
Primary	3	3	6 (46.2)
Worn mask	6	7	13 (100.0)
Washed hands before meals	6	7	13 (100.0)
Social distancing	4	6	10 (76.9)
No contact greetings	6	7	13 (100.00)
Applied sanitizer frequently	4	3	7 (53.8)
Smoking habit	5	7	12 (92.3)
Oral tobacco	4	3	7 (53.8)
Occupation			
Veg vendor	4	3	7 (53.8)
Shop keeper	2	3	5 (38.6)
Tea stall keeper	-	1	1 (7.6)
Suspected place of acquisition			
Work place	5	6	11 (84.6)
Market	1	-	1 (7.7)
Others	-	1	1 (7.7)
Admitted to hospital	1	2	3 (23.1)
Month of acquisition			
May 21	3	2	5 (38.5)
Jun 21	3	5	8 (61.5)
Quarantine of contacts			
Home	21 contacts of 6 affected	23 contacts of 7 affected	13 (100.0)
Center	-	-	-

metaplasia justifying increased levels of ACE2 secreted in the lungs of smokers.[22] Goblet cells are the chief source of mucous that renders a prime barricade to inhaled pathogens preventing subsequent invasion and infection. Though it is possible that smoking increases ACE2 expression in the bronchial epithelium facilitating entry of COVID-19, this does not necessarily indicate a higher risk for developing COVID-19 pneumonia.[23] A most up-to-date research demonstrated that increased cumulative smoking in the past was associated with a higher risk of hospitalization and mortality from COVID-19 in a dose-dependent manner.[24] Exchange/sharing of half-burnt tobacco-stick or hand-smothered tobacco-quid essentially appears an overriding risk for COVID-19 acquisition undoubtedly.

PPM provides essential defensive shield against COVID-19 convincingly but their optimality calls for congruent application in the lore of contextual reflection like discomfort, indistinct communication, shortness of breath, drinking tea, and smoking.[25] Most gratifyingly children were spared and all afflicted, recovered back to well-being. Cases surfaced mostly in May–Jun 21 among the subjects, substantiated by national report.[20]

The study showcased the heterogeneity of risks of COVID-19 acquisition prevailing in Kolkata slums in the context of low SES and education, poor civic facilities, crunch of family space and physical environment, sharing of public toilet and water point, marginal workers subsisting on meagre income, working in over-populated high-exposure zone including high-risk cultural dictum that perhaps precludes social distancing and safe-self-sustenance conscience to all possible extent. All these factors contribute, to an extent, higher COVID-19 risk in Kolkata slums through these unattended socio-graphics facilitating social contracting of COVID-19.

The occurrence rates of COVID-19 infection among the communities are reciprocally analogous as well as similar to the state/national figures. Such reflection perhaps indicates that COVID-19 occurrence has probably been influenced by 3rd world socio-graphics in India with millions living

below poverty line, therefore conveys necessity for further exploration.

Limitations of the study

This has been a restricted work among the residents of 2 different slums in south Kolkata for a specific time period during heightened surveillance situate with controlled mobility and out-reach under strict containment; therefore the outcome needs cautious interpretation for comparison.

CONCLUSION

In spite of the confines, the information generated, visualizes that incessant & unfailing observance of PPM could be most pertinent in this sine-die situation till attainment of vaccination of sizeable population. Health education on safe-self-sustenance considering heterogeneity of causes by tweaking and tuning the awareness parameters would be sine-qua-non to avert COVID-19 undeniably. Further research in similar directions may be of assistance to figure out future line of approach to stall the dread along with vaccination.

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A novel design silicone oil removal cannula

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ABSTRACT

Background: Silicone oil, which is one of the most commonly used endotamponades in vitreoretinal surgery, is removed after a certain period of time in most cases. In this study, we present our results with a unique cannula that provides effective and safe silicone oil removal. **Aims and Objectives:** To assess the aids and success of silicone oil removal with a novel 23-gauge cannula for the patients who underwent pars plana vitrectomy and silicone oil injection before. **Materials and Methods:** 72 eyes of 64 patients who operated by the same surgeon (FA) between May 2017 and May 2019 were involved in the study. The primary indications were proliferative diabetic retinopathy in 46 (63.9%) eyes and retinal detachment in 26 (36.1%) eyes. Phacoemulsification and intraocular lens implantation (23 eyes), membrane peeling (23 eyes), internal limiting membrane peeling (5 eyes), and argon laser endo-photocoagulation (37 eyes) performed in the same session. Furthermore, perfluorocarbon remnants aspirated in 9 eyes and 17 eyes needed suturing. Descriptive statistical analyses achieved by SPSS 10.5 statistical software. **Results:** The mean follow-up time was 11.7 + 2.5 months (between 3 and 23 months), and the mean age was 61.4 + 8.52 years (between 44 and 69 years). 1000 centistokes (cSt) silicone oil was removed from 61 (84.7%) eyes, and 5000 cSt silicone oil was removed from 11 (15.3%) eyes. The mean removal time was 2.04 + 0.1 min for 1000 cSt silicone oil and 5.11 + 0.3 min for 5000 cSt silicone oil. 4 re-detachment and 3 vitreous hemorrhage observed in follow-up period. Post-operative silicone oil remnants were not detected in any patient. **Conclusion:** The unique 23-gauge cannula provides silicone oil removal without any conjunctival cut-down and sclerotomy enlargement. Thus, it reduces the duration of surgery and post-operative recovery period.

Key words: 23-G pars plana vitrectomy; A novel cannula; Silicone oil removal

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INTRODUCTION

Silicone oil began to be used in vitreoretinal surgery in 1962. Over time, it has become commonly used intraocular tamponade.[1] Using silicone oil, quick visual rehabilitation is achieved. However, it can cause severe complications such as cataract, glaucoma, or keratopathy in aphakic eyes specially. The severity of complications are proportional to the duration of its stay in the eye.[2,3]

As a general opinion, to minimize the long-term complications of silicone oil; it is recommended to remove tamponade after achieving its purpose and stable retinal condition.[4] Both anterior and posterior segment approaches can be performed for silicone oil removal.

Aims and objectives

To described a new cannula and approach for silicone oil removal through a 23-G sclerotomy that provides additional endolaser photocoagulation and epiretinal membrane peeling without incision enlargement.

MATERIALS AND METHODS

72 eyes of the 64 patients who underwent active silicone oil removal in Dunyagoz Eye Hospital (Istanbul/Turkey) between May 2017 and May 2019 were included in the study. Pars plana vitrectomy and 1000 or 5000 centistokes (cSt) silicone oil injections were performed for proliferative diabetic retinopathy in 46 (63.9%) eyes and retinal detachment in 26 (36.1%) eyes, respectively. Moreover, 23 (31.9%) eyes had cataract formation.

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None of the silicone oil-related complications such as glaucoma or keratopathy were observed. The reason for silicone oil removal in clinically stable retinas was to avoid silicone oil associated long-term complications. None of the eyes were hypotonic. The best-corrected visual acuity (BCVA) was measured on the Snellen chart and converted to a logarithm of the minimal angle resolution (LogMAR) equivalents for statistical analyses. Goldmann applanation tonometer was used for intraocular pressure (IOP) measurement. Slit-lamp examination findings of the cornea, conjunctiva, and anterior segment structures were noted. For funduscopic examination binocular indirect ophthalmoscope and contact widefield lenses were used. Before the silicone oil removal, all retinas were attached and stable.

The design of the study was approved by Institutional Review Board. All patients signed an informed consent before the surgery. and all data collected in agreement with Declaration of Helsinki.

Post-operative IOP changes were studied with SPSS 10.5 for windows statistical software, and $P<0.05$ was considered statistically significant for all of the analyses.

Description of the special cannula

A silicone cap and ring around the brass tip of the special 19-gauge silicone oil removal cannula helps it to seal to the funnel shaped 23-gauge valveless trocar. Together with the connected tubing system, this special cannula can be assembled to viscous fluid extraction section of the vitrectomy machine (Figure 1). Once the cannula is inserted to the aperture of the valveless trocar, by the high vacuum it is sucked into the trocar obtaining a tight seal. Therefore, silicone oil can be extracted safely, quickly, and without interruption (Figures 2 and 3).

Surgical technique

The surgeries were performed under posterior subtenon injection of 5 mg bupivacaine HCL and 60 mg lidocaine HCL.

Leica surgical microscope and BIOM non-contact system were used for visualization. Silicone oil removed through 23-G sclerotomies with the special cannula and D.O.R.C Associate® Dual System.

Pupilla was dilated with tropicamide 1% and cyclopentolate 1% before surgery. 5% povidone-iodine drops were used for sterilization.

After the first inferotemporal sclerotomy was created, a 23-G infusion cannula was inserted into the trocar. The infusion bottle height set to 65 cm before placing superotemporal and superonasal 23-G trocars. One of the trocars which were combined with the cannula was valveless. To prevent post-operative leakage, all trocars were inserted to the pars plana through 45° scleral tunnels after

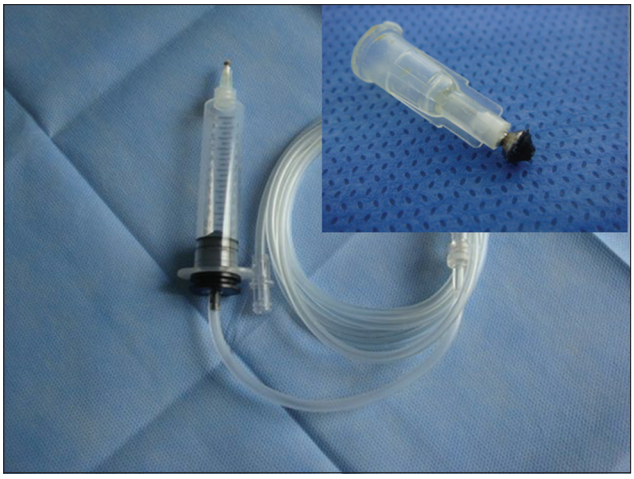

Figure 1: Hand-piece and cannula tip

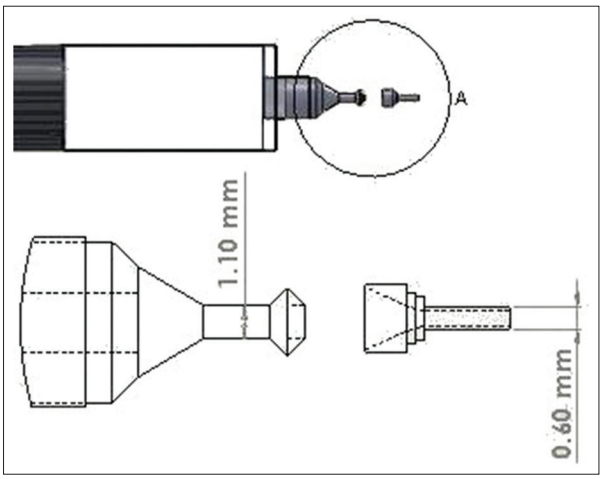

Figure 2: Drawing of the cannula tip and trocar

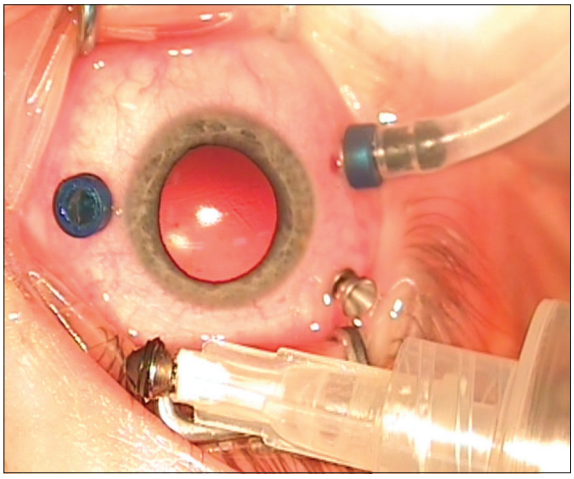

Figure 3: Appearance of the silicone cannula tip intraoperatively

sclerotomies had created using microvitreoretinal knives. The bottle height increased to 90 cm. 1000 or 5000 cSt silicone oils started to be aspirated using a 500–600 mmHg vacuum with the new design cannula which has a special 19-G silicone cap and ring around the brass tip that is compatible with the valveless trocar. As the silicone oil bubble gets smaller and smaller, the cannula was just removed to let the passive passage of the last tiny bubble (Figure 4).

Subsequently, to remove all silicone oil remnants; the air-fluid exchange was performed in all eyes after putting the valve of the trocar. After retinal examination with a 23-G light probe, endolaser photocoagulation was performed in 37 eyes and perfluorocarbon remnants aspirated was performed in 9 eyes. In addition to silicone oil removal, membrane peeling in 23 eyes and ILM peeling in 5 eyes was also performed in the same session.

Phacoemulsification and intraocular lens (IOL) implantation was performed in 23 eyes. Initially, 23-G trocars were inserted as explained above. Phacoemulsification surgery was performed by "phaco chop" or "stop and chop" technique later. The anterior chamber was filled with an ophthalmic viscosurgical device. After silicone oil removal, foldable acrylic posterior chamber IOL was implanted into the capsular bag so that posterior capsule integrity was preserved in all combined phacoemulsification and silicone oil removal cases.

The height of bottle was decreased to 60 cm at the end of the surgical procedure. The infusion line was temporarily shut down before each trocar was removed. Adequate pressure with a cotton swab was applied to the sclerotomies and the infusion line was activated after each trocar had been removed. Finally, the infusion cannula was removed. The sclerotomies were evaluated for fluid/gas exchange related bleb formation and wound leakage. The conjunctival massage was performed on sclerotomies to avoid post-operative hypotony. Suture placement was needed in 17 eyes.

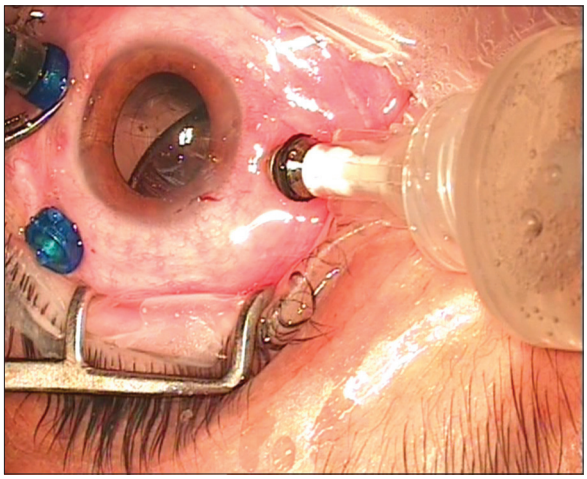

Figure 4: Combined phaco and silicone oil removal with the special cannula

The operation was terminated after subconjunctival steroid and antibiotic injection.

The patients were examined on post-operative 1st day, 1st week, 1st month, 6th months, and 1st year. Silicone oil removal times were recorded during surgeries.

RESULTS

The mean age of 37 (57.8%) male and 27 (42.2%) female patients was 61.4 + 8.52 (44–69) years. Average time between silicone oil injection and intake was 9.36 + 5.14 months. Mean post-operative follow-up time was 11.7 + 2.5 (3–23) months. There were 1000 cSt silicone oil in 61 eyes and 5000 cSt silicone oil in 11 eyes. Average silicone oil removal times were 2.04 + 0.1 minutes for 1000 cSt silicone oil and 5.11 + 0.3 min for 5000 cSt silicone oil (Table 1).

Mean pre-operative IOP was 15.47 + 3.01 mmHg, and mean post-operative IOPs on 1st day, 1st week, and 1st-month visits were 14.15 + 3.91, 15.43 + 2.52, and 16.12 + 0.85, respectively. There was no significant statistical difference between pre- and post-operative IOP levels (P>0.05). Choroidal detachment, endophthalmitis, and post-operative cataract development were not observed in any patient. There was no clinically significant macular edema or corneal decompensation in any case. 4 re-detachment and 3 vitreous hemorrhages were detected in the follow-up period. Silicone oil remnants were not observed in any patient. None of the patient had decrease in visual acuity. BCVA improved in 42 (58.3%) eyes and not changed in 30 (41.7%) eyes. Mean pre-operative BCVA was 1.6 + 0.2 LogMAR, and the mean post-operative BCVA was 1.3 + 0.2 LogMAR at the last visit.

DISCUSSION

Many techniques have been described for intraocular silicone oil removal.[3,5,6] Silicone oil can be removed by active suction or can be flowed out passively[3] through a sclerotomy port[6] by filling vitreous cavity with balanced salt

Table 1: Silicone oil removal times

Type of silicone oil	1000 cSt	5000 cSt
Number of patients	61 (84.7%)	11 (15.3%)
Removal time	2.04+0.1 min	5.11+0.3 min

cSt: Centistokes

solution. Silicone removal with anterior segment approach has severe limitations in case of additional vitreoretinal procedure required.

If compared with the 19-G or 20-G surgery techniques, one of the most important advantages of the 23-G vitreoretinal surgery system is allowing less sutureless surgery. Sutureless surgery eliminates the localized inflammation and irritation that suture materials can cause. Therefore, it provides post-operative inflammation lower and patient rehabilitation faster.[7-9] We performed silicone oil removal in aphakic, pseudophakic, and phakic eyes under posterior subtenon's anesthesia. During the surgeries, suture placement was needed in 17 (23.6%) eyes.

Qin et al.,[10] reported 29 min average surgery time to remove 5000 cSt silicone oil by moving back a 10-mL syringe connected to a 20-G Vasocan cannula through corneal incision in aphakic eyes. Another study reported that active silicone oil removal takes 4–5 min.[6] Yildirim et al.,[11] reported 9 min average surgical time for passive removal of 1300 cSt silicone oil and 7.6 min average surgical time for active aspiration of 5700 cSt silicone oil. Kapran and Acar[12] reported 3.31 + 1.14 min and 10.27 + 0.48 min mean removal time for 1000 cSt and 5000 cSt silicone oil, respectively, with their new 25-G active drainage technique. Kapran and Acar[13] attempted to remove 5000 cSt silicone oil through 25-G transconjunctival sclerotomies passively. However, they did not use their own techniques to remove the 5000 cSt silicone oil, as the passive removal of the oil takes a very long time.

Oh et al.,[14] reported average silicone oil removal time 1.49 ± 0.43 min for 1000 cSt silicone oil and 7.12 ± 1.27 min for 5700 cSt silicone oil, respectively, with a 23 gauge transconjunctival cannula using an external vacuum pump.

In our study, active removal of 1000 cSt silicone oil through 23-G trocars was achieved in a mean period of 2.04 + 0.1 min and 5.11 + 0.3 min in 5000 cSt silicone oil which is rather short. In addition, there was not any statistically significant difference between pre- and post-operative IOP levels ($P>0.05$). Similar to our findings, previous studies with 25-G and 23-G systems also reported that differences between IOP in the 1st postoperative day were statistically insignificant.[7,15,16]

In this study, we did not experience any endophthalmitis. We share the same opinion with Lakhanpal et al.,[15] who stated that proper preparation with povidone-iodine is essential to reduce the risk of contamination of the vitreous with conjunctival flora throughout trocar insertion.

Reported re-detachment rate after silicone oil removal varied between 6% and 33%.[3,17-19] We reported 4 (5.5%) re-detachment cases in our study which is slightly lower than literature knowledge.

In our study, visual acuities either improved or remained unchanged in all patients. BCVA improved in 42 (58.3%) eyes and remained unchanged in 30 (41.7%) eyes. Mean pre-operative BCVA was 1.6 for LogMAR and mean post-operative BCVA at last visit was 1.3 for LogMAR.

Limitations of the study

In our study, the efficacy and safety of a unique silicone oil removal cannula was investigated and the results were compared with the literature knowledge. Different silicone oil extraction techniques could be performed for the different patient groups and a comparison could be made with the cannula we presented in the study.

CONCLUSION

Consequently, this novel design special cannula provides a simple, safe, and quick approach for active removal of 1000 cSt or 5000 cSt silicone oil through a 23-G valveless trocar. In addition, since it allows the operation to be performed through a small scleral incision, it increases the postoperative patient comfort and shortens the recovery time.

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FA- Concept and design of the study, prepared first draft of manuscript and revision of the manuscript; **DD-** Interpreted the results; reviewed the literature and manuscript preparation, statistical analysis and revision of the manuscript.

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Role of JIGSAW method of teaching in improving clinical diagnosis among final year medical students – A prospective observational study

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ABSTRACT

Background: The Jigsaw method is a form of cooperative learning, in which students are actively involved in the teaching-learning process that improves the long-term retention of acquired knowledge. **Aims and Objectives:** The objective of this study was to assess the knowledge acquired by students using the Jigsaw learning method in Internal Medicine. **Materials and Methods:** A prospective observational study was conducted with 100 students. The acute coronary syndrome was taken for 1 h as a didactic lecture, and a pre-test was conducted. The students were divided into five groups and were put for the intervention "Jigsaw." The pre- and post-test were conducted, and feedback was collected from the students. Paired t-test was used to perform analysis of pre- and post-test. Feedback evaluation was done by a 5-point Liker scale. $P<0.05$ was considered statistically significant, and the data were analyzed using CoGuide software. **Results:** The mean pre-test score was 8.44 ± 2.33 ranged (3–14) and the mean post-test score was 11.03 ± 2.07 (ranged 6–15). The difference of 2.39 (95% CI: 2.19–2.59) increase in marks post-test after the Jigsaw method was statistically significant ($P<0.001$). The satisfaction level was 50–55% on the Likert scale based on the questionnaire given. There was a significant improvement in the post-test scores of the students after Jigsaw. **Conclusion:** The Jigsaw method improved knowledge in the short-term by engaging students in group work and motivation to learn. Overall response based on the questionnaire about the Jigsaw method was positive.

Key words: Diagnosis; Internal medicine; Medical students; Programed learning; Teaching

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INTRODUCTION

The year 2019 will be marked as a year of change in the medical curriculum of all the medical universities of India. More than 20 years have passed since the existing regulations on graduate medical education, 1997, were notified, necessitating a relook at all aspects of the various components in the existing regulations and adapt them to the changing demography, socioeconomic context, perceptions, values, and expectations of stakeholders. The thrust in the new regulations is on the continuation and evolution of thought in medical education, making it more learner-centric, patient-centric, gender-sensitive, outcome-oriented, and environmentally appropriate.[1]

A good teaching method exposes the learners to challenging situations and provides them with opportunities for interaction, consultation, cooperation, discussion, and debate with themselves and their teacher so that they can develop their power of thinking and participation.[2] Cooperative learning is a method of education that has gained a lot of research interest in recent years so that it is called as one of the greatest innovations in the educational system. Cooperative learning is a method of education in

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which the learner is responsible not only for his learning but also for the learning of others. The learners work in small groups to help one another learn the educational content, carry out group projects, and master different subjects by cooperating and consulting with their peers and transferring their knowledge. The main approaches to cooperative learning used in recent decades include Student Team Achievement Divisions, Team-Games-Tournaments, Team Assisted Individualization, and Jigsaw. These methods differ in terms of their structure and the type of learners' responsibilities involved.[3]

Surgical and clinical didactics have traditionally employed lecture-based teaching methods. In recent years, there has been a growing call for more "learner-centered" modalities of instruction in graduate medical education. These "learner-centered" modalities include flipped classrooms, where the learners take a more active role in the learning process. While plenty of published studies have established the effectiveness of flipped classrooms, a few studies have examined their efficacy in surgical resident education.[4] The Jigsaw classroom is one form of these flipped classrooms. Social Psychologist Aronson[5] first designed it in 1971 to help weaken racial divides in forcibly integrated schools. The Jigsaw classroom seeks to make students active participants in the learning process. This method organizes the classroom so that the students are dependent on each other to succeed by breaking classes into groups and breaking assignments into pieces.[6]

A previous study by Charlier et al.,[7] investigated the quality of peer-assisted learning using the Jigsaw method compared to direct teaching by an instructor for learning cardiopulmonary resuscitation (CPR). They have shown that peer-led laypersons' training in basic life support using this model results in a CPR performance quality that is in line with the ERC 2010 guidelines while offering advantages in terms of workload for the instructor and skill acquisition and retention for the learner. The Jigsaw method has not only been shown to build comprehension, but it also encourages cooperatively among students. It is known to improve listening and communication skills. Since 1970, the Jigsaw method has been successfully tried in various areas of education such as elementary or primary education, nursing education, pharmacy, and other fields but less so in medical subjects.[8,9]

Literature search could not yield many published articles on the Jigsaw method for clinical diagnostic teaching for medical students in India. Hence, the present study was implemented to assess the effectiveness of the Jigsaw method over didactic lectures in teaching Internal Medicine among the final year students and to assess the knowledge acquired by students in Internal Medicine after the Jigsaw method of teaching. Although the Jigsaw method can apply to many topics in medical education, we chose to apply this learning technique for clinical diagnosis since this topic highlights problem-solving techniques.

Aims and objectives

- The present study was taken to study the effectiveness of the "Jigsaw method" in combination with a lecture in enhancing cognitive skills in clinical diagnosis.
- To assess the student perception toward cooperative group activities.

MATERIALS AND METHODS

Study design

A prospective observational study.

Study setting

Lecture room of medical college.

Study population

Final year medical college students.

Study period

One month from October 2020 to November 2020.

Sample size and sampling technique

Sample 100 was selected by a convenient sampling method for the feasibility of the study.

Sample size calculation

As per the availability of students, 100 students were considered for the final study.

Ethical and informed consent

The study was approved by the Institutional Ethical Review Board, and before the study started, written informed consent was obtained from the participants.

Inclusion criteria

- Final year medical students
- Present in the class during the study
- Those who have given consent.

Exclusion criteria

- Absent on the day.

Jigsaw technique

Jigsaw learning technique or Jigsaw puzzle constitutes a well-structured cooperative learning technique that is free from many of the problems involved in other learning methods. This and other innovative teaching and learning techniques have been successfully used to improve academic achievement among students. The Jigsaw technique is based

on the philosophy that learning develops best when the subject of study is also taught to others once it is acquired. In the Jigsaw technique, learners are divided into matching groups of four or six. The lesson is then split into the number of persons in each group. Using this classification method means that the content of one part cannot be a prerequisite for any of the other parts, and each part should be independent of the other parts while also covering the lesson plan together. A number is assigned to the members of each group as well as to each subject. For example, subject one is assigned to as a group. At the same time, in other approaches, the tasks are divided among the group members, and each member works independently and only asks for help if needed. Jigsaw learning technique or Jigsaw puzzle constitutes a well-structured cooperative learning technique free from many of the problems involved in other learning methods. This and other innovative teaching and learning techniques have been successfully used to improve academic achievement among students. The Jigsaw technique is based on the philosophy that learning develops best when the subject of study is also taught to others once it is acquired. In the Jigsaw technique, learners are divided into matching groups of four or six. The lesson is then split into the number of persons in each group. Using this classification method means that the content of one part cannot be a prerequisite for any of the other parts, and each part should be independent of the other parts while also covering the lesson plan together. A number is assigned to the members of each group as well as to each subject. For example, subject one is assigned to person one in each group, subject two to person two, and so on. Temporary groups will then be formed. All the members of each temporary group (also called an expert group) work on the same subject; for example, they all work on subject two of the class material. The expert groups consist of three to five members who study and discuss the subjects assigned to them and exchange ideas to gain expertise in them and so that they can explain the subject to other members of the main Jigsaw groups. The teacher and learners agree on a set time. The learners then return from the expert groups to their associated Jigsaw group and teach the subject thus learned to the other members of their group and are also taught all the other subjects learned by the other members of their group. Using this method of teaching provokes the learners' interest in the lessons and improves the social relationship between them.[5]

Data collection

1) Acute coronary syndrome was taken for 1 h as a didactic lecture, and a pre-test was conducted.
2) Then acute coronary syndrome was divided into five parts i) types and etiopathogenesis, ii) clinical features, iii) investigations, iv) management, and v) complications.
3) Students are then divided into five groups and given one topic for each group. Each group is given 1 day time to prepare their topics.
4) Next day, four students from each group are interchanged with other groups in the Jigsaw method so that new groups had four student experts in each part of an acute coronary syndrome.
5) Since the new group has four experts in each part, they are allowed for discussion for 1 h. Experts on a particular topic were enlightening others and vice versa.
6) Post-test was conducted, and feedback was obtained from students.
    - Pre- and post-test questionnaire in the form of MCQs and feedback forms were prepared.
    - Analysis of pre- and post-test was be done by paired t-test.
    - Feedback evaluation was done by 5-point Liker's scale.

Study variables

Student performance on a knowledge-based pre- and post-test was considered as primary outcome variables. Since student perceptions tend to be more subjective, this was used as a secondary outcome.

Statistical methods

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. The association between before and after the intervention of quantitative outcome was assessed by comparing the mean values. The mean differences along with their 95% CI were presented. Paired t-test was used to evaluate statistical significance. $P<0.05$ was considered statistically significant using CoGuide software.[10]

RESULTS

A total of 100 subjects were included in the final analysis. Pre- and post-test results and feedback collected were analyzed.

Demographic characteristics and academic performance

There were 43 (43%) males and the remaining 57 (57%) females. The mean pre-test score was 8.44 in the study population. The mean post-test score was 11.03 in the study population. The improvement of marks was 2.59 in the study population. The mean improvement of percentage was 12.95 in the study population, and the mean feedback score was 40.7 in the study population (Table 1).

Student's perception

The majority of 57% agreed and 38% strongly agreed with the JS helped me to learn better; 50% agree and

22% strongly agreed with the JS covered a wide range of knowledge; 51% agreed and 43% strongly agreed for JS improved communication skills; 55% agreed and 33% strongly agreed for JS improved confidence; 52% agreed and 28% strongly agreed for JS improved clinical reasoning; 52% agreed and 40% strongly agreed with the Study conducted in a well-planned manner; 54% agreed and 33% strongly agreed for Sufficient time was given to learn. JS can be followed in medicine theory class was agree by 54% and strongly agree by 36% and 50% agreed and 33% strongly agreed for JS can be followed in other theory classes, and 41% were neutral, and 21% agreed with the traditional methods should be continued (Table 2).

The individual mean scores for feedback elements were less in JS covered a wide range of knowledge as 3.81 and in traditional methods should be continued as 3.07 compared to other elements mean score which was more than 4. The mean overall feedback scores were 40.7 ± 3.9 in the study population (Table 3).

Assessment of Jigsaw technique

The mean marks of pre-operative were 8.44 ± 2.33 and post-operative was 11.03 ± 2.07. The difference of 2.39 (95% CI: 2.19–2.59) between pre- and post-operative was statistically significant (P<0.001) (Table 4).

DISCUSSION

According to the author's knowledge, this is the first study that used the Jigsaw method to promote active learning and diagnostic reasoning in the lecture room of their medical college. The findings of the present study showed mean pre-test scores as 8.44 ± 2.33 ranged (3–14) and the mean post-test score as 11.03 ± 2.07 (ranged 6–15). The mean difference of 2.39 (95% CI: 2.19–2.59) increase in marks post-test was statistically significant (P<0.001). The students strongly agreed that Jigsaw was helpful for them in understanding the topic in detail. The satisfaction level was 50–55% on the Likert scale based on the questionnaire given. There was a significant improvement in the post-test scores of the students after Jigsaw.

In our study, we have observed that the post-test scores significantly improved after the Jigsaw technique. There was an increase in a mean difference of 2.39 (95% CI: 2.19–2.59) in marks after the Jigsaw method, which was statistically significant (P<0.001). The finding was similar to the quasi-experimental study by Swathi and Rajkumar[11] among second MBBS students where they observed that the post-test scores significantly improved after the Jigsaw technique and 28% of students scored >75% in the pre-test while 78.6% of the students scored >75% in the post-test. P-value was <0.05. Another prospective study by Oakes et al.,[12] in Australia among Medical radiation sciences students showed that marks of the Jigsaw workshop participants compared to workshop non-participants (controls) was higher and statistically significant. The findings of the present study were in contrast to a comparative study between Jigsaw learning method to traditional lecture among first professional year student pharmacists learning about medication therapy management by Wilson et al.,[13] in the United States where, improvement in post-test scores favored the traditional method (P=0.001), and the study found that students seemed to find value in the Jigsaw learning method, but performed better on the post-test knowledge questions when the material was presented using traditional didactic lecture.

In the present study, we took the student's feedback by a questionnaire and found that students had taken this interventional approach with a positive attitude. Many students (n=54, 54%) agreed to incorporate the

Table 1: Summary of the demographic parameter (N=100)

Parameter	Summary
Gender	
Male	43(43%)
Female	57(57%)
Pre-test	8.44±2.33 ranged (3–14)
Post-test	11.03±2.07 ranged (6–15)
Improvement of marks	2.59±2.1 ranged (0–9)
Improvement of (%)	12.95±10.52 ranged (0–45)
Mean feedback scores	40.7±3.8 ranged (32–49)

Table 2: Summary of the response to questionnaire using Likert's scale (N=100)

Parameter	Strongly disagree	Disagree	Neutral	Agree	Strongly Agree
JS helped me to learn better	-	2 (2%)	3 (3%)	57 (57%)	38 (38%)
JS covered a wide range of knowledge	-	13 (13%)	15 (15%)	50 (50%)	22 (22%)
JS improved communication skills	-	-	6 (6%)	51 (51%)	43 (43%)
JS improved confidence	-	-	12 (12%)	55 (55%)	33 (33%)
JS improved clinical reasoning	-	1 (1%)	19 (19%)	52 (52%)	28 (28%)
A study conducted in a well-planned manner	-	-	8 (8%)	52 (52%)	40 (40%)
Sufficient time was given to learn	-	3 (3%)	10 (10%)	54 (54%)	33 (33%)
JS can be followed in Medicine theory class	-	1(1%)	9(9%)	54(54%)	36(36%)
JS can be followed in other theory classes	-	1(1%)	16(16%)	50(50%)	33(33%)
Traditional methods should be continued	12(12%)	14(14%)	41(41%)	21(21%)	12(12%)

Table 3: Summary of mean response to questionnaire (N=100)

Feedback	Mean±SD
JS helped me to learn better	4.31±0.6
JS covered a wide range of knowledge	3.81±0.9
JS improved communication skills	4.37±0.6
JS improved confidence	4.21±0.6
JS improved clinical reasoning	4.07±0.7
A study conducted in a well-planned manner	4.32±0.6
Sufficient time was given to learn	4.18±0.7
JS can be followed in medicine theory class	4.25±0.7
JS can be followed in other theory classes	4.15±0.7
Traditional methods should be continued	3.07±1.1
Mean feedback scores	40.7±3.9

Table 4: Comparison of mean marks in pre- and post-operative (N=100)

Marks	Mean±STD	Mean difference (95% CI)	P-value
Pre-test	8.44±2.33	2.39 (2.19–2.59)	<0.001
Post-test	11.03±2.07		

material into their practice. The finding was similar to a comparative study by Goolsarran et al.,[14] in New York, where all workshop participants (100%) indicated that the workshop content was helpful. A higher percentage of the participants in the Jigsaw intervention group compared to the traditional small group (91% vs. 9%) reported that what they learned from the workshop session would impact future practice (χ^2=32.1, df=1, P<0.001).

In the present study, most of them were (n=57, 57%) female. Females tend to have a more positive attitude than males and are also more willing and more motivated to participate. This finding is in contrast to an educational intervention using the Jigsaw Cooperative-L technique among dental students by Suárez-Cunqueiro et al.,[15] in Spain, where when gender was considered, it was noted that most of the students who did not attend the examination were females, reaching a value of 86% (6 of 7 students).

In the present study, students were divided into five groups and given one topic for each group. Each group is given 1 day time to prepare their topics. The next day four students from each group are interchanged with other groups in the Jigsaw method so that new groups had four student experts in each part of an acute coronary syndrome. Since the new group has four experts in each part, they are allowed for discussion for 1 h, and experts of particular topics enlightened others and vice versa. This same strategy was seen in an interventional study among medical students by Uppal and Uppal[16] in Delhi, which had shown that the students learned more things when they worked in groups compared with working individually. Through the group activity, the students not only gained academic knowledge but also learned how to work in collaboration in a group and how each student functions as an individual member of the group, and how other members behave and work in groups. Another quasi-experimental study among nursing students by Sanaie et al.,[17] in Iran concluded that the Jigsaw method provided an opportunity for students to acquire skills such as lecturing in the classroom, time management, setting goals for learning, using examples and teamwork, which increased the self-regulated learning and academic motivation of nursing students.

The Jigsaw classroom is a structured, task focussed class that introduces a lot of material in a short space of time. The caveat for participants is that they learn much more about one element of the topic in the session. Consequently, to balance their understanding across all elements, learners have additional work to do outside the class. The method is suitable as the face-to-face element in a blended learning approach. This is because it allows for discussion and application of the material, so usefully paired with independent reading and reflection.[18]

Limitations of the study

The sample size of the study is small as only half of the batch was involved. The study was conducted on only one topic, and hence the findings should be used cautiously in other fields. The study did not have a control group from the same classroom that was not subjected to the Jigsaw technique, which could hinder the generalizability. The Jigsaw technique is time-consuming and hence requires proper methodology in learning a topic. The efficacy of the Jigsaw method in terms of long-term retention of knowledge acquired needs to be evaluated by further studies among different postgraduate and undergraduate students of other branches.

CONCLUSION

The present study demonstrates that a Jigsaw cooperative learning approach can be an effective instructional method in learning concepts related to clinical diagnosis. Our results suggest that the Jigsaw method is a valid teaching technique as didactic lectures. It emphasized peer teaching, holding each individual accountable for the learning materials, and uses fewer resources while also focusing on the importance of teamwork. Therefore, it can be utilized regularly where faculty time for teaching is limited. It could also be used as part of a library induction, to evaluate resources, or to facilitate a journal club for clinicians or students. Further, research is needed to determine if a combination of didactic teaching and the Jigsaw method enhances increased "soft skills" and retention.

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ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Evaluation of atherosclerosis in patients with chronic kidney disease by measuring carotid intima media thickness: An observational study from a tertiary care center in India

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ABSTRACT

Background: Chronic kidney disease (CKD) is associated with a substantial cardiovascular mortality and morbidity. Besides other factors, accelerated atherosclerosis plays a significant role in this. Carotid intima media thickness (CIMT) is an index of systemic atherosclerosis. By measuring the CIMT with the help of B mode ultrasound at common carotid artery, the overall atherosclerotic burden in CKD patients can be estimated. Accordingly patients at increased risk of premature mortality can be identified so that timely intervention can be taken. **Aims and Objectives:** The aim of the study was to measure the CIMT at the level of common carotid artery by B mode ultrasound for estimation of atherosclerotic burden in patients with CKD. **Materials and Methods:** It is a hospital based observational cross-sectional study involving 70 patients carried out in the department of General Medicine of Medical College and Hospital, Kolkata for a period of 1 year. Patients were selected on the basis of certain inclusion and exclusion criteria. They were evaluated based on clinical history, disease duration, physical examination findings and certain investigation parameters such as complete hemogram, renal function tests, serum potassium, lipid profile, urinalysis, urine for albumin-creatinine ratio, ultrasonography of kidney-ureter-bladder, and CIMT value as measured by B mode ultrasound of carotid artery. The data collected were analyzed with a suitable statistical analysis software package. Range, frequencies, percentage, mean, standard deviation, and P value were calculated. $P<0.05$ was taken as significant. **Results:** The study showed a strong correlation between CIMT and BMI ($r=0.533$, $P<0.001$). CIMT for serum triglyceride levels (≥ 150 mg/dl) were significantly ($P<0.001$) high in patients (mean $\pm$ SD $= 1.45 \pm 0.559$) mg/dl in comparison with serum triglyceride levels (<150 mg/dl) (0.98 $\pm$ 0.380 mg/d). Patients with high cholesterol of ≥ 200 mg/dl have a higher CIMT of 1.56 ± 0.574 with $P<0.001$. There is statistically significant relation of LDL with respect to mean CIMT as $P<0.001$ at 1% level of significance. Hence, mean CIMT is more in LDL (≥ 130) than in LDL (<130). CIMT for HDL levels (<40 mg/dl) were high in CKD (mean $= 1.53 \pm 0.518$ mg/dl) patients compared to HDL levels (≥ 40 mg/dl) (mean $= 10.88 \pm 0.291$). It was found that mean CIMT was higher in the later stages of kidney disease (Stage 3B, 4 and Stage 5) as compared to early stages (Stages 1, 2, and 3). We also found that the Mean CIMT (1.214 ± 0.531 was higher in patients with CKD compared to sonographically defined normal value (<0.9 mm). Hence, CKD patients who have traditional risk factors for atherosclerosis such as higher BMI, higher serum total cholesterol level, higher serum triglyceride level, higher serum LDL level, and lower serum HDL level have a higher value of CIMT. **Conclusion:** B-mode ultrasound is a non-invasive sensitive tool for assessment of CIMT. Since CKD is associated with accelerated atherosclerosis and subsequent increased cardiovascular mortality, this modality may help us to identify patients with atherosclerotic burden so that timely intervention can be taken to reduce future cardiovascular complications in CKD patients.

Key words: Atherosclerosis; Carotid intima media thickness; Chronic kidney disease; Dyslipidemia; Ultrasonography

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INTRODUCTION

Chronic kidney disease (CKD) is a serious condition associated with premature mortality, decreased quality of life, and increased health-care expenditures.[1] Many patients with CKD have cardiovascular disease. They die prematurely from this condition instead of surviving long enough to face dialysis or transplantation. Patients with CKD tend to have an excess of traditional risk factors for cardiovascular disease, such as hypertension, diabetes, and hyperlipidaemia.[2-4] Renal disease also promotes cardiovascular injury by different mechanisms. These include dysregulation of calcium and phosphate metabolism, vascular calcification, anemia, dyslipidemia, hyperhomocysteinemia, and endothelial dysfunction leading to accelerated atherosclerosis. The atherosclerosis is often asymptomatic. So a direct examination of vessel wall is necessary to detect affected individuals in early stages. According to International Atherosclerosis Project, the process occurs simultaneously in carotid, cerebral, and coronary artery.

Carotid intima-medial thickness (CIMT) is well-established index of systemic atherosclerosis.[5,6] Studies have shown that this is an independent predictor of cardiovascular mortality in CKD population.[7-11] Measurement CIMT of the common carotid artery by B-mode ultrasound is a suitable non-invasive method to visualize the arterial walls for monitoring the early stages of atherosclerotic process.[12-15] It is also helpful to decide the appropriate method of treatment, either surgical or medical in patients with carotid artery stenosis.[16-18]

Aims and objectives

The aim of the study was to identify the at risk population among CKD patients with regard to atherosclerotic burden by assessment of CIMT by B mode ultrasound of common carotid artery.

MATERIALS AND METHODS

This was an observational cross-sectional study conducted in the inpatient and outpatient department of General Medicine, Medical College and Hospital, Kolkata from January 2019 to August 2020. Permission was obtained from the Institutional Ethics Committee.

The study population was clinically stable adult patients of either sexes having CKD coming to Medical college within the stipulated time period (n=70). Focused history taking including the demographic profile of the patients, clinical history with duration of disease, medication history, disease specific therapy, and its duration along with clinical examination was done. Investigations were performed which included complete and clinical examination were done. Investigations including fasting lipid profile, urea, creatinine, potassium, urinalysis study, urine albumin-creatinine ratio (ACR), hemoglobin, USG whole abdomen with kidney, ureter, bladder, and CIMT as measured by USG Doppler study were carried out.

All ultrasound measurements were performed at the Dept. of Radiology, Medical College, Kolkata. CIMT was assessed at three levels on each side: Common carotid artery, bulb, and internal carotid artery. The mean CIMT was defined as the mean of the three CIMT measurements on each side, According to current sonographic criteria, a normal value is defined as CIMT <0.9 mm. In addition, the number and size of carotid atherosclerotic plaques were also assessed. The patients were categorized on the basis of age, sex, disease severity, and common risk factors. CIMT values obtained were correlated with the above parameters along with markers of atherosclerosis. The data collected were tabulated in a master chart.

Statistical analysis

Data analysis was performed with a commercially available statistical analysis software package (SPSS 27.0 for Windows; SPSS; Chicago, IL, USA). The Range, frequencies, percentage, mean, standard deviation, and P value were calculated. P<0.05 was taken as significant.

RESULTS

70 patients were included in the study. All of them had CKD (according to National kidney foundation). The patients were studied for CIMT in relation with the different stages of CKD and also with cardiovascular risk factor such as age, sex, BMI, and dyslipidemia.

Out of 70 CKD patients, 39 (55.7%) were males, and 31 (44.3%) were females. Baseline characteristics of cases are mentioned in Table 1. The mean value of these characteristics are shown in Figure 1. The distribution of age and sex of the patients are shown in Table 2 and Table 3 respectively. The same is shown in pictorial form in Figure 2 and Figure 3 respectively. The mean age of study population was 58.37±12.193 years (34–90 years). Mean CIMT level was 1.214±0.531mm.

In present study, when CKD patients were staged, then 14 (20.0%) of the patients were in the Stage 5, 11 (15.7%) were in Stage 4. About 64.3% of the patients were in early stage of kidney disease (Stages 1, 2, and 3A and 3B) (Table 4 and Figure 4).

Table 1: Baseline characteristics of different parameters

Baseline parameters	Mean±SD
Age (years)	58.37±12.193
BMI	26.46±2.376
Total Cholesterol (mg/dl)	207.10±50.632
Triglycerides (mg/dl)	164.57±42.732
LDL (mg/dl)	132.01±46.519
HDL (mg/dl)	40.91±9.270
VLDL (mg/dl)	32.94±8.551
Carotid intima media thickness (mm)	1.214±0.531
UREA (mg/dl)	72.97±58.567
CREA (mg/dl)	2.83±3.511
Urine albumin-creatinine ratio (mcg/mg)	185.24±137.315
K+ (mmol/L)	4.16±0.766
Hb (g/dl)	10.75±1.749
GFR value (ml/min/1.73 m)	42.74±29.269

Table 2: The distribution of age of chronic kidney disease patients

Age	Frequency	Percent
≤40 years	4	5.7
41–60 years	42	60.0
61–80 years	20	28.6
>80 years	4	5.7
Total	70	100.0

Table 3: The distribution of sex of chronic kidney disease patients

Sex distribution	Number of patients	Percent
Female	31	44.3
Male	39	55.7
Total	70	100.0

Table 4: Distribution of the subject according to stages of CKD

CKD stages	Number of patients	Percentage
Stage1	6	8.6
Stage 2	16	22.9
Stage 3A	5	7.1
Stage 3B	18	25.7
Stage 4	11	15.7
Stage 5	14	20.0
Total	70	100.0

CKD: chronic kidney disease

Table 5: Distribution of mean CIMT according to (eGFR) stage of CKD

Stages of CKD	Mean CIMT
Stage1	1.026 mm
Stage 2	1.15 mm
Stage 3A	0.92 mm
Stage 3B	1.27 mm
Stage 4	1.19 mm
Stage 5	1.42 mm
Correlation coefficient (−0.169)	

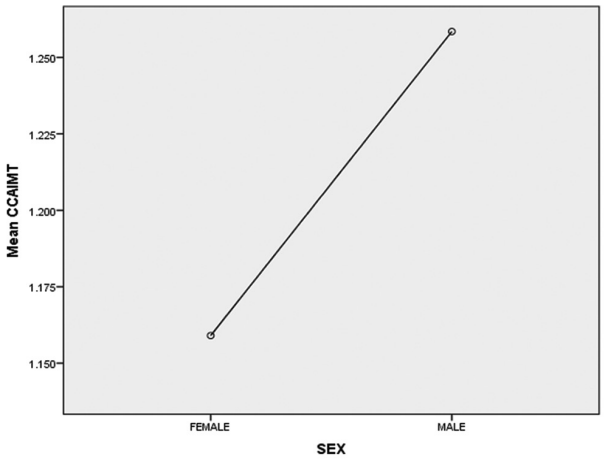
P-value (0.163) (NS) (P<0.05→significance). CKD: chronic kidney disease, CMIT: Carotid intima media thickness

Table 6: Significance of different parameters (AGE) with respect to mean carotid intima media thickness

Parameter	Category	Mean±SD	P-value
AGE	≤40 years	1.21±0.187	0.639
	41–60 years	1.23±0.546	
	61–80 years	1.21±0.563	
	>80 years	1.50±0.463	

Table 7: Significance of different parameters (SEX) with respect to mean carotid intima media thickness

Parameter	Category	Mean±SD	P-value
SEX	Male	1.26±0.543	0.441
	Female	1.16±0.519	



From Table 5, it is observed that there is no direct co-relation of the CIMT and eGFR (CC=−0.169 [P=0.163]). However, CIMT values are more in later stages of CKD (Stage 3B, 4, and 5) compared to early stages (Stages 1, 2, and 3A) (Figure 5).

From Table 6, it is observed that there is statistically no significant relation of categories of age with respect to mean CIMT as the P>0.05, at 5% level of significance. Mean CIMT is maximum in the age group more than 80 years and minimum in the age group of 61–80 years.

From Table 7, it is observed that there is statistically no significant relation of Sex with respect to mean CIMT as the P>0.05, at 5% level of significance. Mean CIMT is more in male than in female.

From Table 8, it is observed that there is statistically significant relation of BMI with respect to mean CIMT

Table 8: Significance of different parameters (BMI) with respect to mean carotid intima media thickness

Parameter	Category	Mean±SD	P-value
BMI	Non-obese	1.18±0.484	0.044*
	Obese	1.67±0.915	

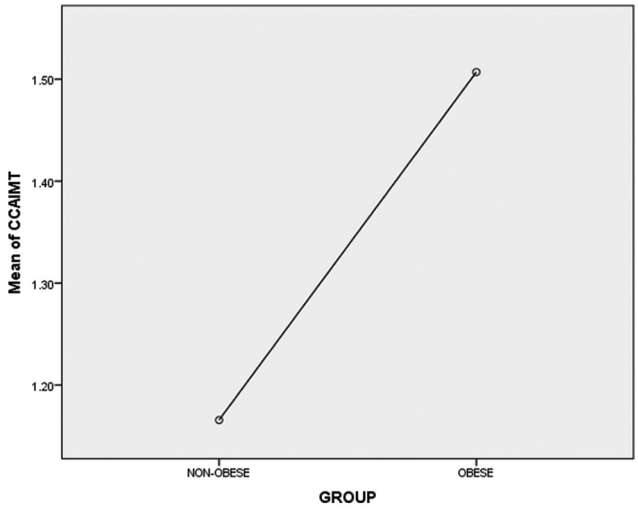
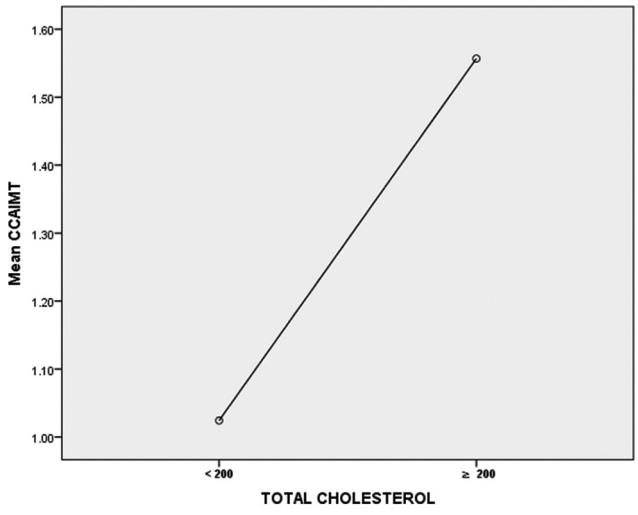


Table 9: Significance of different parameters (TC) with respect to mean carotid intima media thickness

Parameter	Category	Mean ± SD	P-value
TOTAL CHOLESTEROL	<200	1.02 ± 0.399	P < 0.001
	≥200	1.56 ± 0.574	

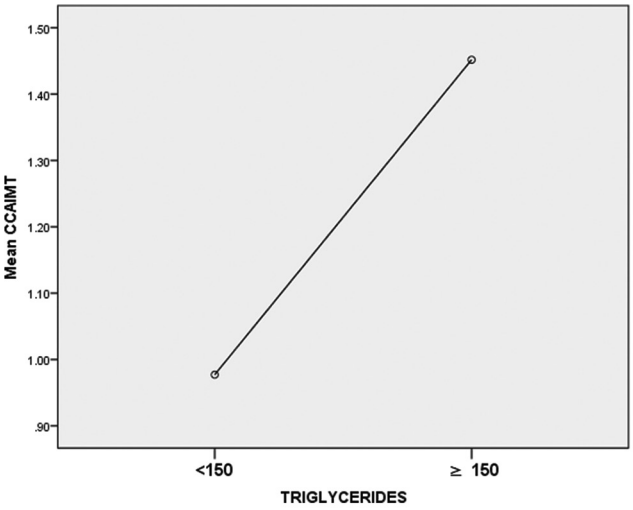


as the p<0.05, at 5% level of significance. Mean CIMT is more in obese than in non-obese.

From Table 9, it is observed that there is statistically significant relation of total cholesterol with respect to mean CIMT as the P<0.001 at 1% level of significance. Mean CIMT is more in TC (≥200) than in TC (<200).

Table 10: Significance of different parameters (TG) with respect to mean carotid intima media thickness

Parameter	Category	Mean±SD	P-value
Triglycerides	<150	0.98±0.380	P<0.001
	≥150	1.45±0.559	



From Table 10, it is observed that there is statistically significant relation of triglycerides with respect to mean CIMT as the P<0.001 at 1% level of significance. Mean CIMT is more in TG (≥150) than in TC (<150).

From Table 11 it is observed that there is statistically significant relation of HDL with respect to mean CIMT as the P<0.001 at 1% level of significance. Mean CIMT is more in HDL (<40) than in HDL (≥40).

From Table 12, it is observed that there is statistically significant relation of LDL with respect to mean CIMT as the P<0.001 at 1% level of significance. Mean CIMT is more in LDL (≥130) than in LDL (<130).

From Table 13, it is observed that there is statistically significant relation of VLDL with respect to mean CIMT as the P<0.01 at 1% level of significance. Mean CIMT is more in VLDL (≥130) than in VLDL (<130).

When univariate correlation analysis between CIMT and study parameters of age, BMI, serum total cholesterol levels, serum triglyceride levels, serum HDL-C levels LDL-C and VLDL-C, urine ACR, etc., was performed in CKD patients in Table 14, significant correlation (P<0.05) of CIMT was found with BMI, serum cholesterol and serum triglyceride levels, and serum HDL-C levels LDL-C and VLDL-C.

Table 11: Significance of different parameters (HDL) with respect to mean carotid intima media thickness

Parameter	Category	Mean±SD	P-value
HDL	<40	1.53±0.518	P<0.001
	≥40	0.88±0.291	

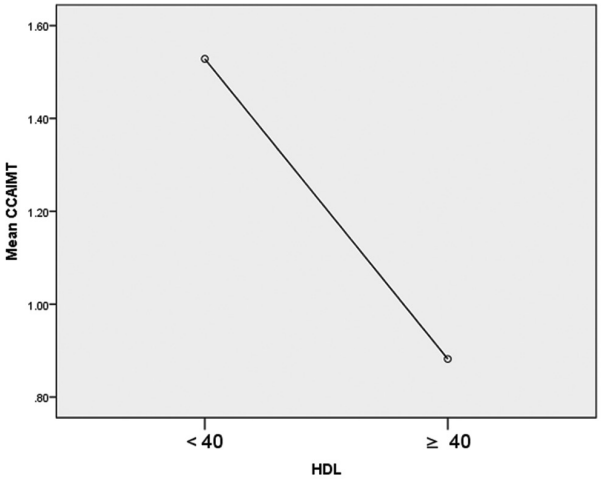


Table 12: Significance of different parameters (LDL) with respect to mean carotid intima media thickness

Parameter	Category	Mean ± SD	P-value
LDL	<130	0.97 ± 0.378	P < 0.001
	≥130	1.60 ± 0.517	

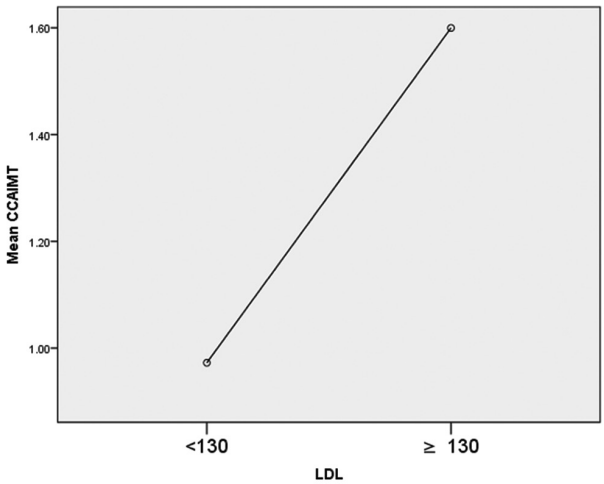


Table 13: Significance of different parameters (VLDL) with respect to mean carotid intima media thickness

Parameter	Category	Mean±SD	P-value
VLDL	<30	1.01±0.396	0.005*
	≥30	1.37±0.572	

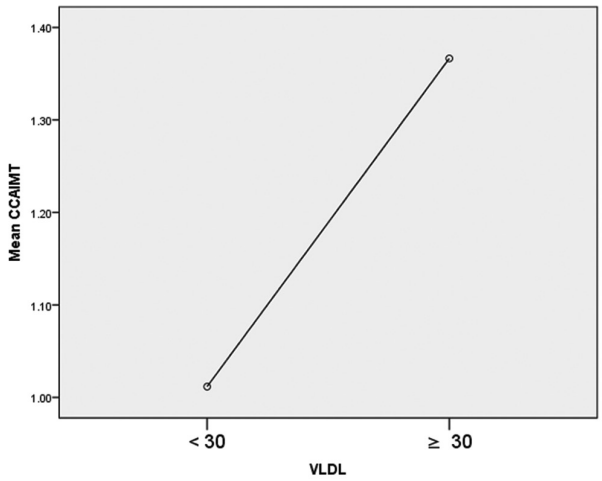


Table 14: Significance of correlation of parameters with carotid intima media thickness

Parameter	Correlation coeff (r)	P-value
Age (years)	0.096	0.431(NS)
BMI	0.533	P<0.001(HS)
Total Cholesterol (mg/dl)	0.564	P<0.001(HS)
Triglycerides (mg/dl)	0.419	P<0.001(HS)
LDL (mg/dl)	0.550	P<0.001(HS)
HDL (mg/dl)	−0.541	P<0.001(HS)
VLDL (mg/dl)	0.412	P<0.001(HS)
UREA (mmHg)	0.011	0.930 (NS)
CREA (mg/dl)	0.046	0.705 (NS)
Urine albumin-creatinine ratio (mcg/mg)	0.077	0.527 (NS)
K+ (mmol/L)	0.120	0.323 (NS)
Hb (gms/dl)	−0.035	0.777 (NS)
GFR value (ml/min/ 1.73 m)	−0.169	0.163 (NS)

DISCUSSION

70 patients were included in our study. All of them had CKD (according to National kidney foundation). The patients were studied for CIMT in relation with the different stages of CKD and also with cardiovascular risk factor such as age, sex, BMI, and dyslipidemia. In our study, the mean age of patients was 58.37±12.19 years (range 34–90 years). Maximum number of subject was 42 (60%) in age group of 41–60 years. Out of 70 CKD patients, 39 (55.7%) were males and 31 (44.3%) were females. Mean CIMT level was 1.214±0.531 mmHg. The present study showed strong correlation between CIMT and BMI (r=0.533, P<0.001). In relation to sex, this study showed that males had higher CIMT values than females. According to lipid profile, this present study observed that CIMT for serum triglyceride levels (≥150 mg/dl) were significantly (P<0.001) high in patients (mean±SD =1.45±0.559) mg/dl in comparison with serum triglyceride levels (<150 mg/dl) (0.98±0.380 mg/d). So also, patients with high cholesterol of

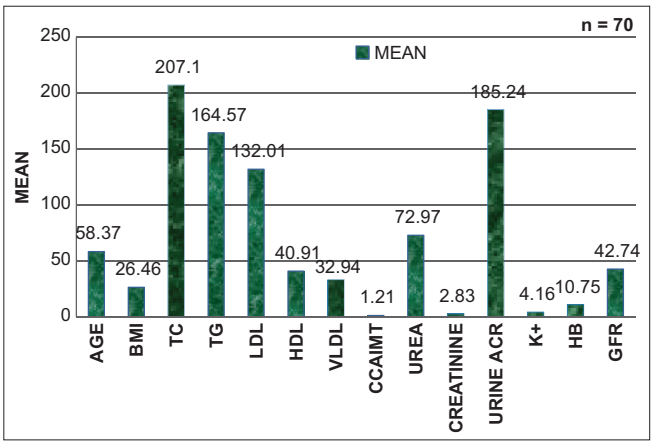


Figure 1: Mean value of baseline characteristics of different parameters

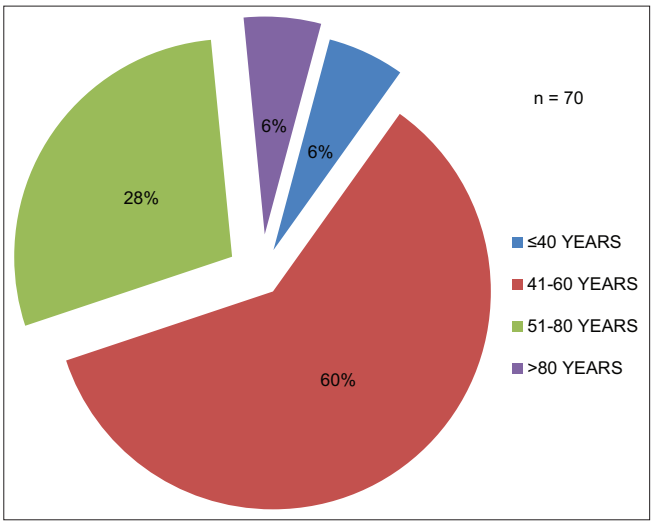


Figure 2: Age distribution among CKD patients. CKD: Chronic kidney disease

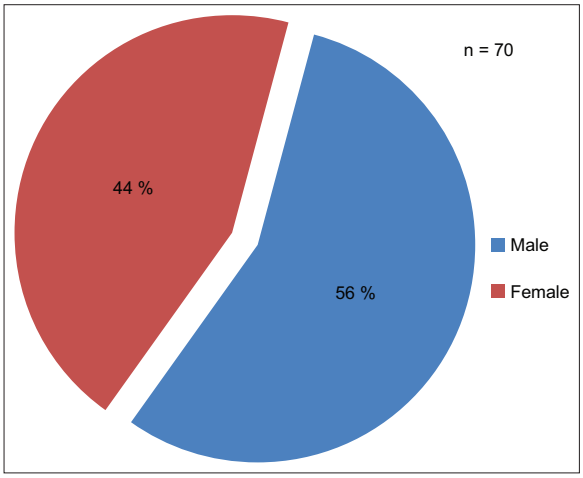


Figure 3: Sex distribution among CKD patients. CKD: Chronic kidney disease

≥200 mg/dl have a higher CIMT of 1.56±0.574 with P<0.001. There is statistically significant relation of LDL with respect to

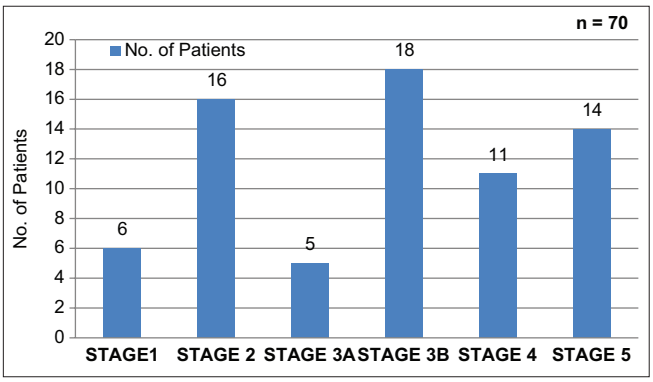


Figure 4: Distribution of the subject according to stages of CKD. CKD: Chronic kidney disease

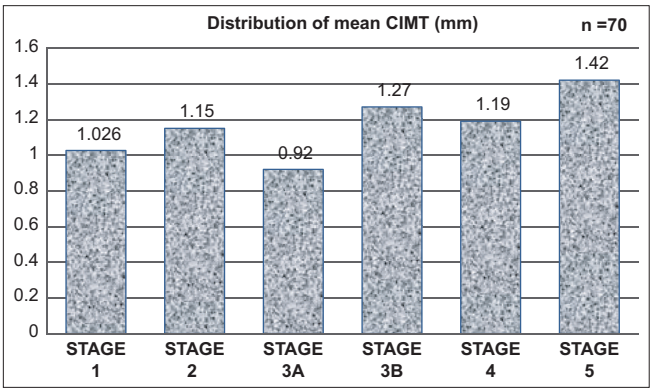


Figure 5: Distribution of the of mean CIMT according to stages of CKD. CIMT: Carotid intima media thickness, CKD: Chronic kidney disease

mean CIMT as the P<0.001 at 1% level of significance. Hence, mean CIMT is more in LDL (≥130) than in LDL (<130). In the present study, CIMT for HDL levels (<40 mg/dl) were high in CKD (mean=1.53±0.518 mg/dl) patients compared to HDL levels (≥40 mg/dl) (mean=10.88±0.291). It was found that mean CIMT was higher in the late stages of kidney disease (Stage 3B, 4 and Stage 5) as compared to early stages (Stage 1, 2, and 3A). According to age, our study showed that mean CIMT is higher in older patients with mean age of 58.37±12.93 years. In present study, the mean CIMT level was 1.214±0.531 mm. According to current sonographic criteria, a "normal" CIMT value is referred as <0.9 mm. Thus, the CIMT was higher in patients with CKD compared to sonographically define normal value.

Limitations of the study

A possible limitation of our study was the small sample size attributed to the stringent inclusion criterions of our study design. This was an institution based study and this could have introduced selection bias. The patients were followed up for the short term outcomes and this assessment may not represent the long-term therapeutic benefits. Extended follow-up period could have changed our outcomes. No blinding was done at any step in the study.

CONCLUSION

From this study, we can conclude that CKD patients who have traditional risk factors for atherosclerosis such as higher BMI, higher serum total cholesterol level, higher serum triglyceride level, higher serum LDL level, and lower serum HDL level have a higher value of CIMT. B-mode ultrasound is a non-invasive sensitive tool for assessment of CIMT. It can help us to identify patients with atherosclerotic burden so that timely intervention can be taken to reduce future cardiovascular complications in CKD patients.

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Consent was taken from the patients for conducting the study after approval from the Institution Ethics Committee (IEC). We would like to express our gratitude to our patients for their cooperation. We would also like to thank the department of Radiodiagnosis, Pathology and Biochemistry for logistics support.

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ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

A study of association between heart failure with preserved ejection fraction with hypertension and diabetes mellitus

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ABSTRACT

Background: Heart failure is a common clinical entity which we come across in our daily practice and accounts for significant mortality and morbidity. The basic pathophysiology lies in the inability of the heart to pump adequate blood (output) to meet the demands of circulation/tissue or can do so only at the expense of elevated left ventricular filling pressure. Among various types of heart failure, heart failure with preserved ejection fraction (HFpEF) is still a poorly understood entity and several comorbidities such as hypertension, diabetes, coronary artery disease, obesity, and CKD are common association of HFpEF. Diabetes causes heart failure by increasing the risk of CAD and by direct injury to myocardium (cardiomyopathy). Hence, in this cross-sectional observational study, we assess the cardiovascular risk factors such as hypertension and diabetes mellitus in association with HFpEF. **Aims and Objectives:** This study aims to establish the hypothesis that hypertension and diabetes mellitus are associated with a predictor of HFpEF. **Materials and Methods:** Ninety patients were selected. NTproBNP, HbA1C, FBS, PPBS level, and blood pressure was measured and echocardiogram was performed to assess ratio of transmitral flow velocity and annular velocity (E/E′); left ventricular end-diastolic pressure; and left ventricular ejection fraction (LVEF). **Results:** The mean age was 64 ± 7. Forty-two (46.67%) were men and 48 (53.33%) were female. Hypertension was present in 73 (81.11%) and diabetes in 44 (48.89%). E/E´, a parameter of LV diastolic function, showed positive correlation to both risk factors in study ($r = 0.653$, $p < 0.001$). Linear regression indicated that E/E′ (β-coefficient = 0.845, $p < 0.001$) was significantly associated with the presence of risk factors. **Conclusion:** The data show that the prevalence of HTN and DM is significantly higher in patients with HFpEF and establishes a strong association between duration of HTN and DM with symptomatic HFpEF.

Key words: Heart failure with preserved ejection fraction; Diastolic heart failure; NTproBNP; Ventricular ejection fraction; Diabetes complications; Hypertension.

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INTRODUCTION

Heart failure is a clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood, which, in turn, leads to the cardinal clinical symptoms of dyspnea and fatigue and signs of heart failure, that is, edema and rales.[1] Based on underlying mechanism, it could be divided into heart failure with preserved ejection fraction (left ventricular ejection fraction [LVEF] >50%, that is, heart failure with preserved ejection fraction [HFpEF]) or heart failure with mid-range ejection fraction (LVEF 40–49%, i.e., HFmrEF) or heart failure with reduced ejection fraction (LVEF <40%, i.e., HFrEF).[2] The number of cases of HFpEF has been increasing in the Western countries and consists more than 50% of total heart failure hospitalizations. The prevalence of HFpEF sharply increases with advancement of age, with a female predominance.[3] There are limited data on heart failure in

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Indian population. Comparative data from Asian Heart Failure Registry showed that Indian patients with HFpEF were younger with mean age of 63.4 years in males and 46.4 years in females. Risk factors included hypertension (40.3%) and DM (28.8%). It has also been proved that HFpEF is prognostically as bad as HFrEF.[4]

Aims and objectives

To study the prevalence of HTN and DM in HFpEF.

MATERIALS AND METHODS

It was a prospective observational study among patients visiting outpatient department and IPD of Jagannath Gupta Institute of Medical Sciences and Hospital, a Medical College near Kolkata from 2020 to 2021 seeking advice in the Gen Medicine Dept. The study was pre-approved by Institutional Ethics Committee and the study was conducted after obtaining permission accordingly. Sample size was 90 patients between 30 and 90 years both male and female.

The risk factors in study, that is, hypertension and diabetes were based on the following criteria

1. Hypertension, that is, systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg at least on two occasions or receiving antihypertensive drug
2. Diabetes, that is, history of type 2 diabetes diagnosed with American Diabetic Association criteria, that is, symptoms of diabetes plus random blood glucose concentration more than or equal to 200 mg/dl or, fasting plasma glucose more than or equal to 126 mg/dl or, glycosylated hemoglobin more than or equal to 6.5% or, 2 h plasma glucose more than or equal to 200 mg/dl during an oral glucose tolerance test or were on medications for diabetes.[5]

Inclusion criteria

1. The diagnosis of HFpEF has been made based on the following criteria[6,7]
   - Signs and symptoms of heart failure by clinical examination
   - LVEF >50% by echocardiography
   - Echocardiographical evidence consistent with structural or functional anomaly including left diastolic dysfunction/increased left ventricular filling pressure or raised serum NTproBNP.
2. Age more than 30 years and <90 years.

Exclusion criteria

1. Presence of structural heart diseases, for example, hemodynamically significant valvular heart disease, prosthetic valve replacement, H/O HOCM, arrhythmias, implanted pacemaker, post-CABG, or peripheral vascular diseases
2. Pre-existing renal disease/CKD (eGFR < 60 ml/min)
3. History of cocaine or heroin use in the past 6 months
4. History of significant alcohol intake
5. Body mass index (BMI)<18.5 or >40
6. Severe anemia (Hb < 8 g %).

The patients who satisfied inclusion and exclusion criteria have been identified and included in this study. Proper history including demographic details, specific comorbidities, duration of HTN and DM, and medication details was taken and detailed clinically examination was done. For further clinical evaluation, a 12-lead ECG with long rhythm strip, straight X-ray skiagram of chest, and routine blood investigations such as complete blood count, renal function test, glycosylated hemoglobin, fasting plasma glucose, and ser. NTproBNP was performed.

Finally, transthoracic echocardiogram was performed with M-mode, 2D (two-dimensional), Doppler, and tissue Doppler imaging using standard techniques. At first, the following parameters were measured by M-mode: Interventricular septal thickness, left ventricular posterior wall thickness, end-systolic dimension of left atrium (LAD), and left ventricular internal diameter (LVID) at end diastole (LVIDd) and end systole (LVIDs). The LVEF was estimated by 2D approximation and wall motion abnormalities were noted, if any. Next, the following LV diastolic function parameters were measured by recording transmitral flow velocity using Doppler echocardiography, that is, peak early-diastolic transmitral flow velocity (E), peak late-diastolic transmitral flow velocity (A), deceleration time, and E/A ratio. Then, tissue Doppler echocardiography was performed at medial mitral annulus. Peak early (E') and late (A') diastolic mitral annular velocities and their ratio (E'/A') were measured. The ratio of transmitral flow velocity and annular velocity (E/E') was calculated to assess LV end-diastolic pressure (LVEDP) which was used as a parameter of LV diastolic dysfunction. Elevated filling pressure was based on E/E' ratio>10. Diastolic dysfunction was classified into four grades as per ASE guidelines[8] as tabulated (Table 1).

Statistical analysis

Quantitative data thus obtained have been analyzed and exported to statistical software SPSS V.27-2020 for proper interpretation. The continuous variables will be presented as mean±standard deviation, performed by Student's t-test or variance analysis. Percentage analysis was used to describe distribution of demographic variables. The association between HFpEF with diabetes and hypertension was obtained by Chi-square test separately and binary logistic regression analysis was done between predictor variable and dichotomous variable (hypertensive/diabetic or not). P<0.05 was considered as statistically significant.

Table 1: LV diastolic dysfunction as per LV relaxation, filling pressures, and 2D and Doppler findings[9]

Echo parameter	Normal	Grade I	Grade II	Grade III
LV relaxation	Normal	Impaired	Impaired	Impaired
LAP	Normal	Low or normal	Elevated	Elevated
Mitral E/A ratio	≥0.8	≤0.8	>0.8 to<2	>2
Average E/e' ratio	<10	<10	10–14	>14
Peak TR velocity (m/s)	<2.8	<2.8	>2.8	>2.8
LA volume index	Normal	Normal or increased	Increased	Increased

RESULTS

A total of 90 patients between 30 and 90 years both male and female who met the inclusion criteria were selected by simple random sampling. Majority belonged to the age group of 60–70 years with mean age 64±7 years. Forty-two (46.67%) were men and 48 (53.33%) were female. Hypertension was present in 73 (81.11%) and diabetes in 44 (48.89%) patients. Majority had ejection fraction between 55 and 60% and mean was 58.3±5.3%; mostly with normal or near normal systolic function. The elevated mean LVMI indicated LV hypertrophy and decreased mean E/A indicated LV diastolic dysfunction, often produced by hypertension or diabetes. Mean E/E' was 9.78±4.4. All variables were normally distributed by Kolmogorov–Smirnov goodness-of-fit test other than LVEF, E/A, E'/A', and E/E'.

Grade-2 (DD2) diastolic dysfunction patients were maximum in number (44, i.e., 48.89%) followed by Grade-1 (DD1) diastolic dysfunction (38, i.e., 42.22%), and only eight persons (i.e., 8.89%) had Grade-3 (DD3) diastolic dysfunction (Figure 1). The prevalence of comorbidities in study (i.e., hypertension or diabetes) is progressively increasing along with the severity of diastolic dysfunction (from Grade-1 to Grade-2) to a fact that all patients having DD-3 were having at least one comorbidity and most of them have both (Figure 2). Apart from this, age of the patient and duration of hypertension/diabetes seemed to be an important determining factor.

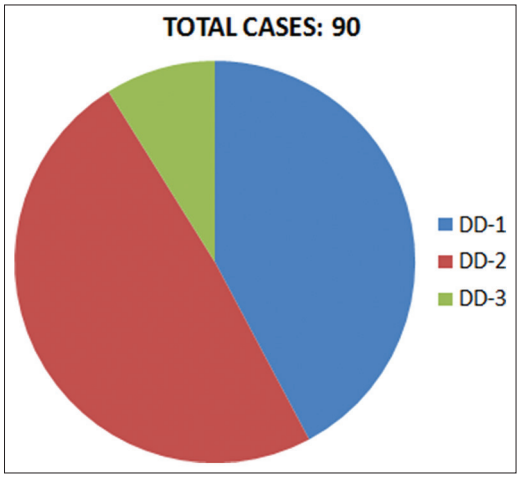

Figure 1: Severity of diastolic dysfunction

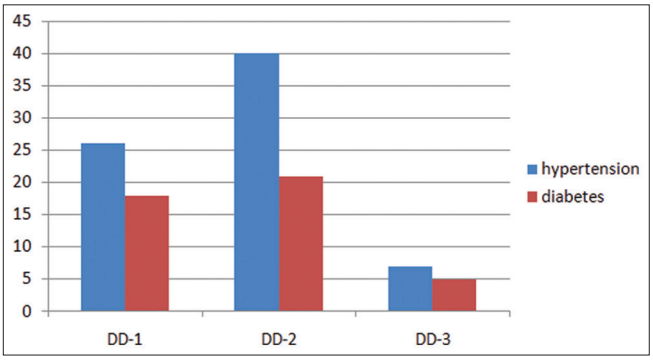

Figure 2: Comparison of number of cases

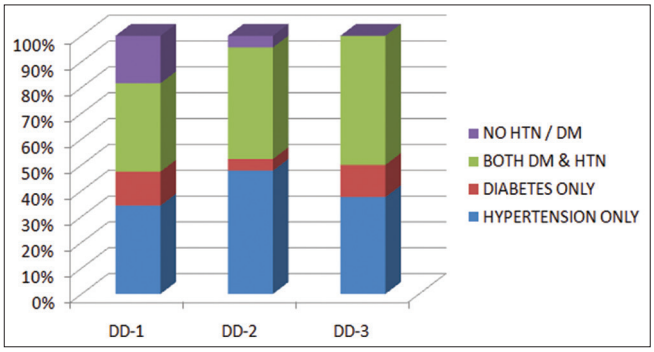

Figure 3: Relative prevalence of comorbidity with severity of diastolic dysfunction

DISCUSSION

In our study, high prevalence of hypertension (and also diabetes) in HFpEF was the most significant finding and signifies a strong etiological association (Figure 3). Patients having longer duration of HTN/DM or having both together were shown to have advanced DD with elevated LVEDP along with advancement of age. These findings are consistent with other large scale trials where hypertension has been identified as the commonest risk factor[10] presenting in 50–90% of patients of HFpEF, and prevalence is even more than that of HFrEF.[11,12] To study individual etiological association of HTN/DM with HFpEF, we also excluded certain other confounding risk factors such as chronic kidney disease, atrial fibrillation, and coronary artery disease which are a complication of HTN/DM itself and also being an important risk factor for HFpEF.[13,14]

Limitations of the study

E/E´ was measured at septal mitral annulus. However, some studies recommended measuring velocities of lateral mitral annulus or averaged velocities of lateral and septal mitral annulus.

The inherent variability of risk factors such as alcohol intake, smoking, exercise, medications, and other unknown variables was not included in the study.

Finally, a multicenter trial with larger population is needed to further investigate etiological factors of HFpEF and its association with comorbidities.

CONCLUSION

Etiology and treatment approach of HFpEF differs from that of HFrEF. Moreover, HTN and DM are the modern day epidemics. Hence, if further studied by multicenter, prospective, longitudinal studies, this association may be used to identify the population at risk for HFpEF and to establish new targets for the management of diastolic dysfunction at the herald of its onset and prevention of symptomatic HFpEF resulting in longer survival and better prognosis.

ACKNOWLEDGMENT

To find out the association between risk factors (i.e. HTN and DM) with the severity of diastolic dysfunction as a predictor of HFpEF.

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SS- Concept and design of study; and guidance for preparation of manuscript; **JB-** Review of literature, preparation of draft, and interpretation of result; **SG-** Collection of data and interpretation of results, preparation of 1st draft.

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Prevalence of hearing impairment and language and cognition delay in very low birth weight babies and their risk factors

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ABSTRACT

Background: Very low birth weight infants are at increased risk of language, cognition delay and also hearing impairment disorder. Identification is essential for early intervention. **Aims and Objectives:** To estimate the burden of language, cognition delay and hearing impairment at 24 months of corrected gestation and to test the association of examination at 6 months and 12 months with the language and cognitive outcome of very low birth weight (VLBW) infants at 24 months and to identify the perinatal and neonatal risk factors for atypical outcome. **Materials and Methods:** It is a prospective cohort study. Consecutive 120 VLBW infants were enrolled in a single centre level III neonatal unit of a teaching hospital. Hearing assessment was done before discharge and 3 monthly. Language and cognitive assessment was done by DASII Scale neu at 6 months and BSIDIII Scale at 12 months and 24 months at neurodevelopmental clinic. Language assessment was further done by REELS-3 Subscale at 24 months. All assessment ages were corrected for prematurity. **Results:** At 24 months 7.8% infants developed Language delay and 4.7% had cognition delay. Four infants developed cerebral palsy at 24 months. Shock in neonatal period had significant association with suboptimal Hearing, Language and Cognitive outcome at 12 months of corrected gestation. **Conclusion:** Early anticipation and early identification of abnormal hearing, language and cognitive outcome of VLBW infants can be used as simple and cost-effective measures for preventing long-term morbidity at resource limited countries.

Key words: Cognitive delay; Hearing assessment; Language delay; Shock; Very low birth weight infants

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INTRODUCTION

The prevalence of speech and language delays ranged from 5% to 8% at the age of 2–4.5 years, while studies of only language delays reported rates of 2.3–19%. Risk factors included a family history of speech and language delays, male sex, and perinatal factors, such as prematurity and low birth weight.[1] Based on the six studies in UK, the prevalence of speech and/or language delays in children ages 2–5 years to be between 5% and 12%.[2] Language delayed children may hold lower-skilled jobs and are more likely to be unemployed than unaffected children.[3]

Approximately, 15 million babies are born very low birth weight, worldwide, each year.[4] Most of the very low birth weight babies are preterm. They have higher degree of language and social communication problems compared to full terms.[5-8]

In about 40% of very low birth weight (VLBW) infants at school age, cognitive impairment had been reported.

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Executive function and attention skills are suboptimal in most of the VLBW infants.[9] The prevalence of impaired hearing in neonates with VLBW is significantly higher than in neonates with normal birth weight because of higher rates of transient middle ear fluid accumulation and conductive hearing loss. Long-term careful monitoring for hearing loss and their audiological management VLBW babies is essential.[10]

1.5% of the VLBW cohort was found to have abnormal prolongation of ABR waveform latency despite normal auditory thresholds, suggesting that even though cochlear function may have been normal; there may have been abnormal ascending brainstem pathways.[11]

Children with hearing loss may have difficulty with hearing and understanding sounds around them and thus leading to speech and communication disorder.

Aims and objectives

1. To estimate the hearing and language and cognition delay among very low birth weight babies.
2. To identify the risk factors of language and cognition delay in VLBW babies.
3. To correlate the predictive value of language evolution at 1 year with language evolution at 2 years of age.
4. To correlate the predictive value of cognition evolution at 1 year with cognition evolution at 2 years of age.

MATERIALS AND METHODS

This is a prospective observational cohort study involving VLBW infants admitted in a level III Neonatal Intensive Care Unit (NICU) during the period of May to September 2016. All the infants discharged from NICU who were <1500 gram at birth were eligible for the study. The infants with chromosomal anomaly, major malformations and those who failed to attend for complete follow-up were excluded. Informed consent was obtained from the parents of VLBW infants eligible for the study. The study was pre-approved by the institutional ethics committee.

Birth weight was taken just after delivery. Antenatal data were collected. Natal and subsequent management were done as per standard protocol.

At 6 months of corrected gestation Developmental Assessment Scale for Indian Infants (DASII), 1 years of corrected age Bayley Scale of Infant and Toddler Development 3rd edition (BSIDIII) and 2 years of corrected age Receptive Expressive Emergent Language Test-3rd edition (REELS-3), was done by professionals who were unaware of case records (Figure 1).

Hearing assessment was done by Oto Acoustic Emission and Screening Automate Auditory Brainstem Response before discharge. Diagnostic Brainstem Evoked Auditory Brainstem Response was done at 3 months of corrected gestation. Subsequent hearing assessment was done at 6 months and 1 year and 2 years of corrected gestation.

Instruments and procedures

DASII

It is Indian adaptation of BSIDII. It is done up to 2.5 years of age. It has two scale: Mental and Motor.

BSIDIII

It is designed to assess the developing and high-risk infants and toddlers and young children aged between 1 and 42 months. It provides coverage of 5 domains: Cognitive, language, motor, adaptive, and social emotional development.

REELS-3

It is used to identify disabilities, condition, impairment that may affect language development. Procedure takes 20 min for the children up to 3 years of age.

Statistical analysis

Linear correlation among two variables was calculated using Pearson correlation and then fit linear regression model to predict the response variables for a given covariate. Chi-square test of association was used to test significance of association between two categorical variables. Statistical software R was used here.

Data had been summarised as mean and standard deviation for numerical variables and count and percentages for categorical variables and analysed by SPSS software version 24.0. Unpaired proportions were compared by Chi-square test or Fisher's exact test as appropriate. Odds ratio was calculated for relative risk with 95% confidence interval value ≤0.05 was considered statistically significant.

RESULTS

Under Linear Linear Regression Analysis, Shock, Perinatal Asphyxia, Hypoglycemia, and Cultutre Positive Sepsis showed significant correlation with Language development at 12 months of age (Table 1). After Multivariate Regression analysis only shock had significant correlation with language development at 12 months of corrected gestation (Table 2). Under Linear Regression Analysis Shock and Perinatal asphyxia got significant correlation with cognitive development at 12 months of corrected gestation (Table 1), but after

multivariate regression analysis none of them showed significant correlation. Under Multivariate Linear Regression analysis only Shock had significant correlation with hearing assessment at 1 years of age (Table 3).

At 24 months of corrected gestation follow-up only 5 babies had language delay and 9 babies were at risk.

Correlation of DASII mental subscale score at 6 month with BSIDIII language subscale score at 12 months of corrected gestation

We plot the scatter diagram of Mental 6 months with the language 1 year. The Pearson product moment correlation is 0.40 implying moderate linear correlation (Figure 2).

Correlation among BSIDIII language subscale at 12 months and REELS-3 language scale at 24 months

Correlation of language subscale at 1 year (assessed by BSIDIII) with 2 years language assessment done by REELS-3 is 0.59 and the scatter plot shown in Figure 3.

Correlation of cognition scale at 12 months of corrected age and cognition scale at 24 months of corrected gestation

Correlation between cognition 1 year and 2 year is 0.51 (Figure 4).

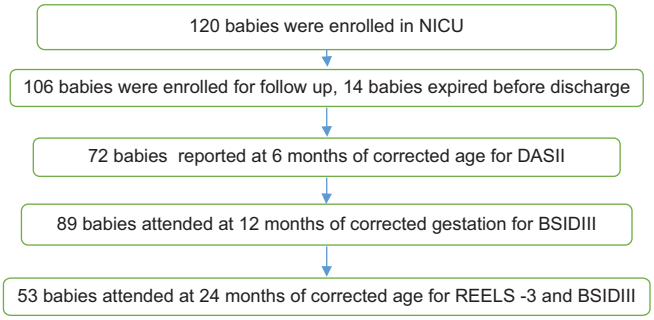

Figure 1: Study flow chart

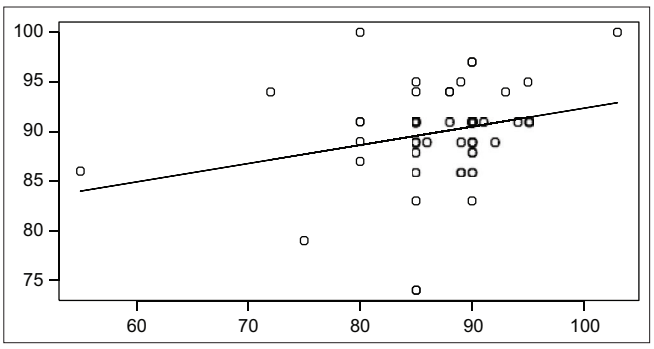

Figure 2: Correlation among mental subscale at 6 months and language subscale at 12 months

DISCUSSION

3.4% of total preterm population in India are VLBW babies. Aram et al.,[12] showed that a higher proportion of VLBW than control children had subnormal language associated with IQ <85, hearing deficits, after increased survival of preterm VLBW babies, there is in need of long term follow-up for language and hearing evolution in a resource limited settings.

In a study from South Africa on neurodevelopmental outcome of preterm infants with mean birth weight and mean gestational age of 1182 grams (SD: 197.78) and 30.81 weeks (SD: 2.67), The BSID III was done at a median age of 16.48 months. Out of 106 babies, 10 babies (9.4%) had language delay, 9 babies(8.5%) had cognition delay.[13] In our study population, the mean birth weight and mean gestational age were 1169.975 grams (SD: 244.3135) and 32.2 weeks (SD: 2.85) respectively and, 5 (7.8%) had language delay and 3 babies (4.7%) had cognition delay at 2 years (corrected gestation) of follow-up.

In our study, shock had got significant and consistent correlation with language and hearing impairment in

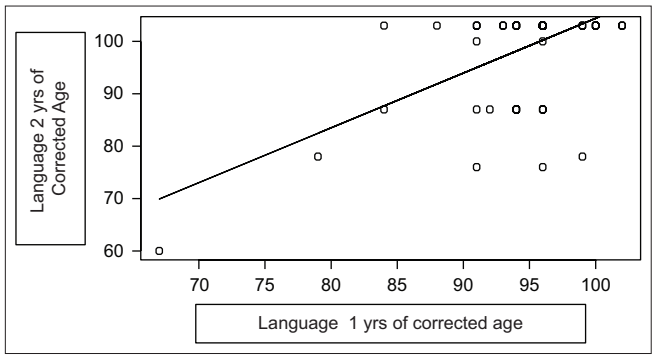

Figure 3: Fitted regression line and scattered diagram of BSIDIII Language Subscale at 12 months and REELS-3 at 24 months

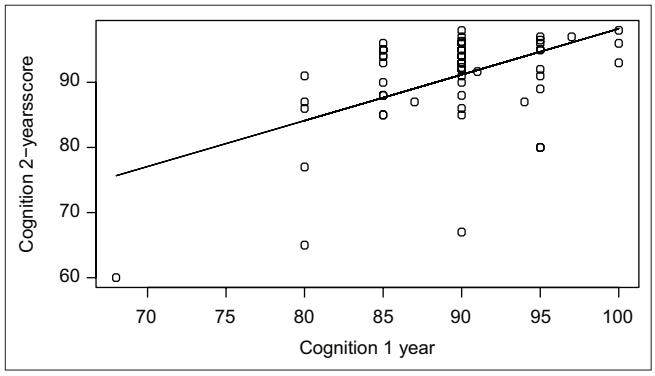

Figure 4: Fitted regression line and scattered diagram of BSIDIII cognition subcale at 12 months and BSIDIII cognition subscale at 24 months

Table 1: Overall characteristics of the VLBW babies and their association with language development

Characteristics	N=120	Correlation with DASII Mental scale at 6 months	Correlation with BSIDIII Language Subscale at 12 months	Correlation with BSIDIII Cognitive Subscale at 12 months	Correlation with Hearing assessment
Birth weight (500–1500 g)	Mean 1169.975 g (SD 244.3135)	0.4816	0.1995	0.0795	0.5396
Gestation (25–40 weeks)	Mean 32.2 weeks (SD2. 85)	0.9233	0.9741	0.9203	0.7903
Antenatal steroid	Nil (40.8%), Partial (33.3%), Full Course (25.8%)	0.2867	0.7617	0.5971	0.4654
Pregnancy Induced hypertension. Other antenatal risk factors are negligible	32 i.e., (26.6%)	0.8336	0.1866	0.0165	0.6866
Small for date	65 i.e., (54%)	0.5708	0.1674	0.3393	0.5141
Mode of delivery	NVD (51.6%), LSCS (48.3%)				
Place of delivery	Inborn (75.8%), Outborn (24.1%)				
Delivery room resuscitation	Routine care (0.083%), Initial steps (51.6%), Bag and Mask (10%), Bag and Tube (15%), Unknown (22.5%)	0.8404	0.3277	0.5499	0.7473
Perinatal asphyxia	No (75%), Yes (25%)	0.5851	0.0386	0.0044	0.4412
Shock	No (86.7%), Yes (13.3%)	0.5395	<0.0001	0.0008	0.0012
Hypoglycemia	No (89.2%), Yes (10.8%)	0.5404	0.0269	0.1742	0.2590
IVH	No (97.5%), (2.5%)				
BPD	No (74.1), Yes (25.8%)	0.6352	0.5541		0.8138
Anaemia requiring blood transfusion	No (91%), Yes (9%)	0.4639	0.1630	0.7347	0.5924
PDA	No (98.3%), Yes (9.7%)	0.6601	0.8818	0.4301	0.1859
Culture Positive Sepsis	No (98.3%), Yes (9.7%)	0.5404	0.0045	0.1219	0.1518

VLBW: Very low birth weight, BSID-III: Bayley scales of infant and toddler development (version III), DASII: Developmental assessment scale for Indian infant, IVH: Intra ventricular haemorrhage, PDA: Patent ductus arteriosus, BPD: Broncho pulmonary dysplasia

Table 2: Multivariate regresion analysis

Corrected age (12 month)	BSIDIII language subscale			BSIDIII cognition		
	St. coeff β	P value	95% CI	St. coeff β	P value	95% CI
Gestational age	−0.171	0.179	−0.052, 0.009	−0.213	0.108	−0.090, 0.009
Birth weight	0.195	0.099	0.000, 0.001	0.189	0.129	0.000, 0.001
Delivery room resuscitation	−0.038	0.742	−0.071, 0.051	−0.073	0.550	−0.127, 0.068
Perinatal asphyxia	−0.169	0.109	−0.349, 0.035	−0.099	0.375	−0.446, 0.170
Shock	0.285	0.006	−0.907, −0.158	−0.107	0.319	−0.902, 0.297

BSID-III: Bayley scales of infant and toddler development (version III)

Table 3: Mental at 6 months and language outcome at 12 months and 24 months by BayleyIII and REELS-3

Subscale	Composite Score (<70) {Abnormal}	Composite Score (70–85){At Risk}	Composite Score (>85) {Normal}	Mean Score	95% CI
Mental (6 months) {DASII}	1 (1.38%)	26 (36.11%)	45 (62.5%)	87.54	86.12–88.96
Language (12 months) {BSIDIII}	1 (1.12%)	7 (7.87%)	81 (91.00%)	89.46	88.35–90.57
Cognition 12 months	2 (2.25%)	24 (26.97%)	63 (70.79%)	89.18	87.86–90.50
Language 24 months {REELS-3}	5 (7.8%)	9 (14%)	50 (78%)	98.61	96.25–100.26
Cognition 24 months	3 (4.7%)	5 (7.8%)	56 (87.5%)	90.78	88.93–92.64

Bayley scales of infant and toddler development (version III), DASII: Developmental assessment scale for Indian infant, REELS-3: Receptive expressive emergent language test-3rd ed..ition

newborn. Goldstein RF et al., also reported significant correlation of language and cognitive outcome in BSID Scales at 24 months of corrected gestation with the duration of perinatal asphyxia and hypotension.[14]

It is observed that there is a mild linear correlation between mental 6 months (DASII) with the cognition 1 year (BSIDIII) and the Pearson product moment correlation is 0.27.

The scatter diagram of Mental 6 months (DASII) with the language 1 year (BSIDIII) showed the Pearson product moment correlation is 0.40 implying moderate linear correlation. Specific terms and words expected from a child during the language test-not familiar to the Indian child resulted in lower scores and significant discrepancy.

Tomasik showed that Preterm VLBW babies have higher chances of hearing loss that term babies. Risk is further aggravated by Shock.[15] We are also getting strong correlation with shock and hearing impairment in VLBW babies.

Limitations of the study

There was good compliance up to 12 months of corrected age but at 24 months of corrected age there was 50% lost to follow-up.

CONCLUSION

Among the all antenatal and natal and postal risk factors neonatal shock and perinatal asphyxia has got most significant correlation with language, hearing and cognition. 6 months assessment of DASII has mild correlation with cognition subscale and moderate correlation with Language Subscale of BSIDIII (assessed at 12 months of corrected gestation). However, 12 months BSIDIII assessment of both the subscale has significant correlation with 24 months assessment.

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Authors Contribution:
SC- Concept and design of the Study, Collected the antenatal histories, did the whole study prospectively, reviewed literature and manuscript preparation, interpreted the result; **SM-** Guide of SC in preparation of concept and design of study and also manuscript preparation; **TKB-** Provided early stimulation after assessment; **TRC-** Assessed the babies by BSID Scale

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Prevalence and risk factors of self-medication in pregnancy: A cross-sectional study from a tertiary care hospital in Eastern India

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ABSTRACT

Background: Self-medication in pregnancy is a common but unsafe practice. There is a possibility of surreptitious exposure of the developing fetus to the teratogenic and abortifacient effects of the drugs. **Aims and Objectives:** In this study, we assessed the prevalence and risk factors of self-medication in pregnant mothers visiting the antenatal clinic in our hospital. **Materials and Methods:** A standard questionnaire seeking information on the socio-demographic profile, clinical characteristics, laboratory data, and knowledge and habits was administered to the pregnant mothers (n = 190). The risk factors of self-medication were determined using Fischer's exact test. $P < 0.05$ was deemed statistically significant. **Results:** The prevalence of self-medication in pregnancy was found to be 6.3%. Low education level ($P < 0.027$), employed women ($P < 0.031$), and history of miscarriage ($P < 0.036$) in the previous pregnancy were the main determinants of self-medication in the present pregnancy. **Conclusion:** The prevalence of self-medication in the study sample was low as compared to contemporary studies. High literacy (94.2%) and easy availability of health facility (98%) may be the possible reasons. Further studies are warranted to confirm the prevalence and risk factors of self-medication in this part of the country.

Key words: Low education level; Pregnancy; Prevalence; Risk factors; Self-medication

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INTRODUCTION

Self-medication is the practice of self-administration of drugs for therapeutic purpose by individuals lacking statutory expertise for the same. The effects, whether beneficial or harmful, are unpredictable, the practice by itself is unscientific and should be discouraged.[1] The implication is, however, altogether different in pregnancy where self-medication is a dangerous practice because it exposes the fetus to the teratogenic and abortifacient effects of the drugs.[2] Teratogenicity refers the capacity of a drug to cause fetal abnormalities when administered to the pregnant mother. The placenta does not provide strict barrier and drugs can come to fetal circulation in greater or lesser extent and may cause harm.[3] Giving birth to an abnormal child may lead to severe and lasting family and social problems. Medications prescribed during pregnancy are normally based on evaluation of their harm to the mother and fetus. In most of the cases, the first choice for treatment of a condition during pregnancy differs from treatment in nonpregnant women. Pregnant women must use the lowest therapeutic dose of medications.[4] The awareness of the risk of self-medication and the prevalence of self-medication in pregnancy, therefore, assumes huge importance in maternal and child health.[2] The prevalence of self-medication in this special population varies with

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respect to the geographical, social, and political conditions prevailing in the different parts of the world.[5] In India, the geo-political structure is variegated across the vast country and social and cultural practices are also diverse.[6] In this study, we have evaluated the prevalence and the indigenous socio-economic factors affecting self-medication in pregnant women visiting the ante-natal department of our hospital situated in a peripheral district in West Bengal.

Aims and objectives

The aims of the study were to estimate the prevalence and determine the risk factors of self-medication in pregnant mothers visiting the antenatal clinic in our hospital.

MATERIALS AND METHODS

Study design

The study was a cross-sectional, observational single center study conducted in pregnant mothers attending antenatal clinic of our institution to estimate the prevalence rate of self-medication in this special population.

Ethical consideration

The study was approved by the ethical committee of the institute. Informed consent was obtained from all patients.

Sample size

Using an expected prevalence of 15% from previous literature, the sample size to estimate the prevalence of self-medication in our population, with 95% confidence and a precision of 5%, was found to be 196.

Data collection and analysis

The pregnant mothers who voluntarily participated and provided written informed consent were interviewed and data on self-medication, demographic, clinical characteristics, and available laboratory investigations were collected. Microsoft Excel was used for data preservation and storage. As per convention, continuous and categorical data were expressed as mean (standard deviation) and percentage/proportion, respectively. Fischer's exact test was used to study the factors associated with the practice of self-medication in the pregnant mothers. The study was conducted in November and December 2018.

RESULTS

190 pregnant mothers participated in the study. The mean age was 23.7±4.8 years. The mean weight and height were 55.2±10.2 kg and 149.5±6.0 cm, respectively. Although 179 of the 190 women were literate (Primary school-52, Middle school-4, High School-21, Senior secondary-79, Graduate-21, and Post-graduate-2), only 12 were working women; while the rest (178) were homemakers. The number of women in the different education groups and the corresponding number of self-medications is shown in Table 1.

The median monthly family income was Rs.7000 (interquartile range - 5000–10000). Data on screening for HIV and hepatitis were available for 144 of the 190 women at the time of interview. None of the women were reactive/positive for the two conditions. 68 women were anemic (Mild anemia-60 and Moderate anemia-8) but none had cyanosis or jaundice. Clubbing and bilateral pedal edema were observed in 19 and 42 women respectively. 106 women were primigravida. The number of women in the first, second, and third trimester at the time of interview was 3, 56, and 131, respectively. 22 women had history of miscarriage. Laboratory data on hemoglobin, total leukocyte count, fasting blood sugar, post-prandial blood sugar, urea, and creatinine were available for 144, 91, 112, 92, 38, and 38 patients, respectively, and the corresponding mean (SD) values were 11.08±1.18 gm %, 7427.66±1934.9 cell/mm^3, 91.84±7.7 mg/dl, 113.28±28.7 mg/dl, 16.98±3.3 mg/dl, and 0.71±0.1 mg/dl. 58 women were aware that self-medication may have harmful effects on the fetus. 5 of them were aware that the practice poses maximum risk in the first trimester. One participant had the perception that third trimester is the most vulnerable period. The total number of women who took self-medication during the present pregnancy was 12. Nine of them belonged to the group of women who were ignorant of the dangers of self-medication. The most common reason for taking self-medication was pain abdomen (06); one woman each took medication for fever and weakness. One woman took vitamin supplements with the belief that vitamins would improve the health of the newborn. Three women took self-medication for non-specific reasons. The medication for pain abdomen comprised of analgesics (03), antacids (02), and proton pump inhibitor (01). About 97.9% (186) of the women were able to avail health-care facility during

Table 1: Level of education and frequency of self-medication

Education	Self-medication		Total (%)
	No (%)	Yes (%)	
Illiterate	10 (5.6)	1 (8.3)	11 (5.8)
Primary school	46 (25.8)	6 (50)	52 (27.4)
Middle school	3 (1.7)	1 (8.3)	4 (2.1)
High school	21 (11.8)	0 (0)	21 (11.1)
Senior secondary	77 (43.3)	2 (16.7)	79 (41.6)
Graduate	20 (11.2)	1 (8.3)	21 (11.1)
Post graduate	1 (0.6)	1 (8.3)	2 (1.1)
Total	178 (100)	12 (100)	190 (100)

Values are expressed as numbers and percentages. Education up to the level of high school was taken as cutoff to dichotomize education level for association with self-medication.

the period of their pregnancy. The mean distance of the facility from the place of residence was 15.7±13.2 km. The factors associated with self-medication in the pregnant mothers are shown in Table 2.

DISCUSSION

In our study, though the majority of women (69.5%) were unaware of the dangers of self-medication in pregnancy, the prevalence of self-medication in the sample was found to be only 6.3%. The figure is on the lower ladder when compared to similar studies (Country, year of publication, and prevalence in percentage) - Mexico, 2018, 21.9%;[7] Tanzania, 2018, 46.24%;[8] Ethiopia, 2018, 15.5%;[9] Malaysia, 2020, 81.4%;[2] Ghana, 2020, 69%;[10] France, 2020, 72%;[11] Brazil, 2020, 27.7%;[12] Nigeria, 2012, 72.4%;[13] and Australia, 2000, 97%.[14] A meta-analysis of 13 studies conducted in 2018 estimated the overall prevalence of self-medication using the random effect model as 32% (95% CI, 22–44%).[5] Our study was not designed to explore the causative factors of the low prevalence of self-medication in pregnant mothers. However, we speculate that the easy availability of hospital (98%), distance of referral hospital <15 km (71%), and high literacy (94.2%) were the possible reasons for the lower prevalence.

About 30% of the participants were aware of the potential harm to the fetus with unsupervised medication. Majority of the women who took self-medication (75%) belonged to the remaining part of the sample who were unaware of the dangers of self-medication. Alani et al., in an observational, cross-sectional study involving a total of 447 pregnant women found that about 82.6% of the women lacked knowledge about the risks of self-medication in pregnancy.[2] The ignorance about the possible harm associated with indiscriminate use of medicines during pregnancy is one of the main reasons behind the high prevalence of self-medication in this vulnerable group. The situation is aggravated in underdeveloped societies where lack of basic health-care facilities, illiteracy, poverty, and traditional beliefs prompts the indigenous communities to seek and resort to unscientific and unsafe practices.[13] While the aim of "Health for all" is an utopia which still remains to be implemented in large underprivileged geographical limits of the world, there is a simultaneous urgent necessity of inculcating habit-based safe health practices through awareness programs and public outreach.[15]

Studies available in the literature have identified numerous factors associated with self-medication in pregnancy. The important ones are - low income, lack of health-care facility, unaffordable medical service, illiteracy, ignorance, and easily available over the counter medicines.[5,7,14] In our study, we

Table 2: Factors associated with the practice of self-medication in pregnant women

S. No.	Factor	Factor category	Self-medication	No self-medication	P value
1.	Education	Education below high school	8	59	0.027
		Education high school and above	4	119	
2.	Employment	Employed	3	9	0.031
		House wife	9	169	
3.	History of miscarriage	Yes	4	18	0.036
		No	8	160	
4.	Age	≤24	6	111	0.541
		>24	6	67	
5.	Religion	Religion 1	10	150	1.00
		Religion 2	2	28	
6.	Monthly income in rupees	≤7000	7	96	1.00
		>7000	5	82	
7.	Medication due to chronic illness	Yes	2	20	0.634
		No	10	158	
8.	Primigravida	Yes	6	100	0.768
		No	6	78	
9.	Number of living children	≤2	11	175	0.231
		>2	1	3	
10.	History of allergy with drugs/food	Yes	4	53	0.754
		No	8	125	
11.	Knowledge of possible harm to child due to self-medication	Yes	4	54	0.758
		No	8	124	
12.	Birth of abnormal baby in previous pregnancy	Yes	2	5	0.064
		No	10	173	
13.	Distance of nearest health facility in Kilometers	≤16	8	127	0.747
		>16	4	51	
14.	Number of days of availability of health facility	≤4	2	14	0.267
		>4	10	164	

Frequency is expressed as counts. Fischer's exact test is used to find association between self-medication and the tested variables. P<0.05 was considered statistically significant.

found that education below high school, employment, and history of miscarriage in the previous pregnancy were associated with higher chances of self-medication in pregnancy (P<0.05). While low education level and ignorance have also been shown to be important determinants of self-medication in pregnancy in the previous studies, the observation that employed women are more likely to resort to self-medication is being newly reported. The possible explanation is that the increased demand of work-life balance may have deprived working women in seeking proper medical advice.[16] Moreover, availability of easy information over World Wide Web may have prompted some of the participants to indulge in the practice of self-medication.[17]

In the past two decades, information technology has penetrated even the remote corners of the Indian society. The dynamics of self-medication and the repercussions thereof are changing with the evolving scenario. A holistic surveillance to ascertain the prevalence, outcomes and the associated factors, is required to judge the true picture of the magnitude of the problem and its remedies.

Limitations of the study

Although the sample size in the study (190) was very close to the estimated sample size (196) to determine the prevalence of self-medication, the event rate of self-medication was not sufficient enough to study the causal factors using Chi-square test or logistic regression. Therefore, the possible risk factors were analyzed using Fischer's exact test. With the existing prevalence of self-medication, a larger sample size will be required to study the determinants of self-medication in pregnancy with greater statistical confidence.

CONCLUSION

The prevalence of self-medication in the study population was 6.3%. Low education level and employment were the two important determinants of self-medication in pregnancy. Further studies are required to corroborate the findings of the study.

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Comparative effectiveness of topical lignocaine nebulization and airway nerve blocks for awake fiber-optic nasal intubation in TM joint ankylosis

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ABSTRACT

Background: Awake fiber-optic nasal intubation is a gold standard management of difficult airway in temporal mandibular (TM) joint ankylosis. **Aims and Objectives:** We compared topical lignocaine nebulization with airway nerve blocks for awake fiber-optic nasal intubation in TM joint ankylosis. **Materials and Methods:** Fifty patients of either gender were randomly allocated into two groups of 25 each. Group I received 10 ml of 2% lignocaine nebulization over a period for 20 min. Group II received bilateral superior laryngeal nerve block and transtracheal recurrent laryngeal nerve block (each with 2 ml of 2% lignocaine). Awake fiber-optic bronchoscopy-guided nasal intubation was done in all patients. All the patients received sedation during the procedure. The intubation time, intubating conditions, vocal cord position, cough severity, and degree of patient satisfaction were recorded. Student's t-test was used to analyze parametric data, while the Mann–Whitney U-test was applied to non-parametric data and Fisher's test to categorical data. $P<0.05$ was considered statistically significant. **Results:** The time taken for intubation was significantly shorter in Group II [110.2 (14.6) s compared with Group I (211.0 [22.3] s) ($P=0.028$ ss). The intubating conditions and degree of patient comfort were better in Group II compared with Group I. Although all patients were successfully intubated, patient satisfaction was higher in Group II. **Conclusion:** Airway nerve block is a better way of anesthetizing airway as compared to nebulization for awake fiber-optic nasal intubation. However, nebulization with lignocaine may be an alternative in situations where nerve blocks are not feasible or may be used as an adjuvant to nerve blocks.

Key words: Fiber-optic; Lignocaine; Nasal intubation; Nebulization; Nerve blocks

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INTRODUCTION

Intubation during general anesthesia in patients with difficult airway poses a risk to the patient and presents challenges for the anesthesiologists.[1,2] An unanticipated difficult airway can jeopardize the life of the patient; administering general anesthesia can be disastrous in such situations if the airway is not secured before induction. Awake intubation using a flexible fiber-optic bronchoscope is considered a gold standard, safe, and relatively simple method for intubating the trachea under direct vision in most situations.[3] The various indications of awake fiber-optic intubation include cervical spine instability, temporomandibular joint ankylosis, facial fractures, partially obstructing laryngeal lesions (e.g. papilloma), and craniofacial abnormalities.[4,5] A pre-requisite for awake fiber-optic nasal intubation is appropriate anesthesia of the nose, oropharynx, larynx, and trachea, to suppress airway reflexes and prevent discomfort during bronchoscopy and intubation. Various techniques are currently used for airway anesthesia including topical anesthesia (with the mucosal application of local anesthetic as a spray, viscous solutions,

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soaked cotton pledgets, and nebulization) or as airway nerve blocks.[6] Despite the availability of these numerous methods for airway anesthesia, few studies have compared them. Airway nerve blocks are frequently used for awake fiber-optic intubation because they provide rapid and deep anesthesia. Nebulization of local anesthetics is another promising technique, in which the airway is anaesthetized completely without the need for multiple painful injections. Therefore, we compared nerve block, which is considered the standard technique for achieving rapid and effective airway anesthesia, with lignocaine nebulization, which constitutes a simple, painless, and comfortable alternative for anesthetizing the airway, before awake fiber-optic bronchoscopy-guided intubation. When carried out under minimal sedation, these techniques help to allay anxiety so that the patient is more cooperative during the procedure.[7] This study was conducted to compare the effectiveness of nebulization of lignocaine and airway nerve block for achieving airway anesthesia before awake fiber-optic bronchoscopy-guided nasal intubation. The primary objective was to compare the intubation time of the two techniques, and the secondary objectives were to assess the quality of airway anesthesia, the degree of patient comfort, and post-operative patient satisfaction.

Aims and objectives

We compared topical lignocaine nebulization with airway nerve blocks for awake fiber-optic nasal intubation in TM joint ankylosis.

MATERIALS AND METHODS

This analytical cross-sectional study was conducted in dental college, an associated hospital of GMC, Srinagar, over a period of 3 years after receiving approval from the ethical committee of our institution. Fifty adult patients (males and females) of 15–60 years of age with temporomandibular joint ankylosis (mouth opening less than 2 finger breadth) with American Society of Anesthesiologist (ASA) physical status of I–II were randomly divided into two groups of 25 each.

Group I: Received nebulization of 10 ml of 2% lignocaine over 20 min.

Group II: Received bilateral superior laryngeal nerve block and transtracheal instillation of 2 ml of 2% lignocaine and 10% lignocaine spray over the bilateral tonsillar, nasal sponge with 2% lignocaine.

Patients with mouth opening greater than 2 finger breadth, patients with cardiovascular diseases, airway diseases, allergy, and oral or nasal mass were excluded from the study. All patients received before procedure sedation (injection midazolam 0.02 mg/kg and fentanyl 1.5 mg/kg body weight) and anti-sialagogue (injection glycopyrrolate 2.5 microgram/kg). Airway was anesthetized by either lignocaine nebulization or nerve blocks. Adequate local anesthesia was confirmed by the heaviness of the tongue in Group I patients and by hoarseness of voice in Group II patients. A 5.0 mm flexible fiber-optic bronchoscope with a flexometallic endotracheal tube with an internal diameter of 7.0 or 8.0 mm (for males and females, respectively) was used. Parameters including intubating conditions, vocal cord position, intubation time, patient comfort, and vital signs were recorded. Vital signs were recorded after 1, 3, 5, and 10 min of intubation. Intubation time was defined as the time from passing the flexible fiber-optic bronchoscope tip through the nostril to the first reading obtained by the capnograph after endotracheal intubation. Scores for intubating conditions, vocal cord position, and patient comfort (was assessed by cough severity and comfort during and after intubation) are graded as shown in Table 1.

After confirmation of endotracheal intubation by capnography, general anesthesia was achieved with propofol (2 mg/kg, IV) and vecuronium bromide (0.1 mg/kg, IV). The day after surgery, a post-operative assessment was done to assess adverse effects such as hoarseness, sore throat, and unpleasant memories.

Statistical analyses

Sample size was calculated by taking the previous data by Gupta et al.,[8] into consideration. The required sample size was 50 patients, with power more than 80% and alpha error of 0.05%. The statistical tests used were Student's t-test for parametric data, the Mann–Whitney U-test for non-parametric data, and Fisher's test for categorical data. The normality of the data was checked using the Shapiro–Wilk test. Continuous variables are expressed as

Table 1: Grading system assessing intubating conditions, vocal cord position, patient comfort, and satisfaction

Grade	Intubating conditions	Vocal cord position	Patient comfort indices		
			Cough severity	Comfort during intubation	Post intubation assessment
Grade 1	Optimal	Glottis open	No cough	No reaction	Cooperative
Grade 2	Suboptimal	Glottis partially open	<2 coughs	Grimacing	Minimal resistance
Grade 3	Difficult	Glottis closed	3–5 coughs	Verbal objection	Severe resistance
Grade 4	Failure		>5 coughs	Defensive movements	

mean (SD) and categorical variables as proportions (%). P<0.05 was considered to be statistically significant. The statistical evaluation was done using SPSS software (ver. 20.0; IBM Corp., USA).

RESULTS

Demographic data were similar between the two groups. There was no significant difference between the two groups with respect to age, sex, body weight, or ASA physical status. The groups were also comparable in terms of airway difficulty, as assessed by modified

Mallampati grade and thyromental distance. However, intubation time in Group II is lesser as compared with Group I and is statistically significant, as shown in Table 2. All patients in both groups were intubated successfully. The mean intubation time for Group II (110.2 [14.7] s) was shorter than that for Group I (209 [22.2] s) (P=0.026) [Table 2]. The intubating conditions for Group II were better than those for Group I (P=0.001). Twenty-three patients in Group II had optimal intubating conditions compared with only two in Group I. Vocal cord position was also more optimal for intubation in Group II compared with Group I (P=0.002). Patient comfort during intubation, as assessed by cough severity (P=0.001) and intubation comfort scores (P=0.012), was higher in Group II than in Group I. Similarly, patient tolerability of endotracheal intubation, assessed post-intubation, was significantly higher in Group II than in Group I (P=0.001), as shown in Table 3. Post-operative patient satisfaction scores for Group II were higher than those for Group I. In Group II, 23 patients rated their experience of awake fiber-optic intubation as excellent or good and none rated it as poor; however, in Group I, two patients rated the experience as poor and none rated it as excellent. The incidence rates of adverse effects, such as post-operative sore throat, hoarseness of voice, and unpleasant memories, did not differ significantly between the two groups.

DISCUSSION

Recent advances in the field of anesthesia have resulted in significant improvements in various aspects of airway management. Since the invention of the flexible fiber-optic bronchoscope in 1966 by Dr. Ikeda et al.,[9] and its subsequent use for endotracheal intubation by Dr. Murphy in 1967,[10] regional anesthesia for the airway has not only rendered awake fiber-optic intubation comfortable and acceptable for patients, but has also afforded anesthesiologists better control over intubation conditions. Several authors have compared different airway anesthesia techniques. In 1990, Webb et al.,[11] compared transcricoid lignocaine injection with use of the spray-as-you-go technique for awake fiber-optic bronchoscopy in 70 adult patients. In 1992, Graham et al.,[12] compared three different methods of providing airway anesthesia during fiber-optic bronchoscopy in 53 patients. In 2000, Kundra et al.,[13] compared nebulized lignocaine 4% with combined regional nerve block for awake fiber-optic nasotracheal intubation in 48 adult patients. Airway nerve blocks are considered a gold standard and include glossopharyngeal nerve blocks, which anesthetize the oropharynx and block the gag reflex; bilateral superior laryngeal nerve blocks, which anesthetize the larynx above

Table 2: Comparison of demographic characteristics between two groups

Patient parameters	Group I	Group II	P value
Age (yr)	44 (10)	44 (10)	0.732
Sex (M/F)	13/12	14/11	0.604
Weight (kg)	64.7 (8.1)	65.9 (11.3)	0.657
ASA physical status 1/2	22/3	21/4	0.366
Modified Mallampati grade 3/4	4/21	3/22	0.264
Thyromental distance (cm) (>6.5/6–6.5/<6)	2/2/21	3/2/20	0.362
Intubation time (seconds)	209.0 (22.2)	110.2 (14.7)	0.026

Data are presented as mean (SD) or number. ASA: American Society of Anesthesiologists

Table 3: Comparison of intubation characteristics between two groups

	Grade 1		Grade 2		Grade 3		Grade 4	
	I	II	I	II	I	II	I	II
Intubation conditions	2	23	12	2	11	0	0	0
Vocal cord position	1	20	14	5	10	0	0	0
Cough severity	1	18	22	4	2	3	0	0
Intubation comfort	1	22	21	3	3	0	0	0
Post-intubation assessment	4	23	20	2	1	0	0	0
Patient satisfaction	0	10	12	13	10	2	3	0

Data are presented as number of patients

the level of the vocal cords and block glottic closure reflex; and transtracheal nerve blocks, which anesthetize the trachea and larynx below the level of the vocal cords and abolish the cough reflex. Airway nerve block provides rapid and deep anesthesia with only small doses of local anesthetic, but a thorough knowledge of regional anatomy, as well as operator skill and experience, is required for correct application. The procedure also involves a risk of accidental intravascular injection and nerve injury, and airway nerve block is not feasible when there is distorted anatomy, such as in cases of massive neck swelling, traumatic injury to the head and neck, and local infection.[6,7] Nebulization of local anesthetics is another technique that deposits fine droplets of local anesthetic directly over the mucosa, thus anesthetizing it and obviating the need for multiple painful injections. Furthermore, this technique requires less detailed knowledge of anatomy, less specialist skills, and less experience; it can also be used in cases of massive neck swelling where nerve block cannot be performed. However, it has some disadvantages including the requirement for large doses of local anesthetic (due to wastage during administration), a higher chance of failure, and a delayed onset of action. In this study, we used 10 ml of 2% lignocaine (200 mg) for nebulization in adult patients, based on a previous study by Sutherland et al.,[14] who found that lignocaine nebulization using a median dose of 512 mg caused toxicity at a plasma concentration above 5 μg/ml in two of their patients, but that a dose of 370 mg did not lead to toxicity. Gjonaj et al.,[15] compared 8 mg/kg and 4 mg/kg lignocaine for nebulization and found both doses to be safe, while Parkes et al.,[6] who used 6 mg/kg lignocaine, did not observe a maximum plasma lignocaine level exceeding 0.45 mg/L in any of their subjects. Because there was no way to measure plasma lignocaine concentrations in our study, we limited the maximum dose of lignocaine to 200 mg. A higher concentration of lignocaine would have reduced the total effective volume reaching the airway mucosa if the dose remained the same. Hence, we deemed it sufficient to use a maximum concentration of lignocaine of 2%, in a possible volume of 10 ml, to produce effective anesthesia without causing lignocaine toxicity. In our study, there was no failure of intubation in either group. The mean intubation time was significantly shorter in the nerve block group; this was similar to the findings of Gupta et al.,[8] who reported a mean intubation time of 123 (46.7) s in a nerve block group and 200.4 (72.4) s in a nebulization group (P=0.047). However, Reasoner et al.,[16] found no significant difference in intubation time between nerve block and topical anesthesia groups, and in both of their groups, the intubation time was longer than in any other study. In contrast to our study, the degree of operator skill with awake fiber-optic intubation was not specified in any previous report. In our study, the intubating conditions were better in Group II compared with Group I, similar to the studies of Webb et al.,[11] and Graham et al.[12] However, Reasoner et al.,[16] and Gupta et al.,[8] found no significant difference in intubating conditions between the groups. It should be noted that no standardized scale for evaluating intubating conditions was used in the previous studies, so we could not directly compare their intubating conditions with those of our study. We compared patient comfort between our two study groups according to cough severity and intubation comfort scores during and after intubation; patient comfort was higher in the nerve block group. This can be attributed to the deposition of local anesthetic in the vicinity of the nerves. However, during nebulization, the local anesthetic is deposited over the mucosa, that is, away from the nerves, so a larger amount of local anesthetic is needed. Furthermore, unpredictable deposition amounts due to wastage can lead to patchy, less effective aesthesia. Gupta et al.,[8] also observed significant coughing in their nebulization group compared with a nerve block group.

CONCLUSION

This study revealed that airway anesthesia using airway nerve blocks is superior to lignocaine nebulization for awake fiber-optic bronchoscopy-guided nasotracheal intubation, in terms of ease of intubation and patient comfort and satisfaction. Nevertheless, lignocaine nebulization may be used as an alternative technique for airway anesthesia when a nerve block is not feasible because we observed no case of failure of awake fiber-optic intubation and no complications related to nebulization.

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Use of umbilical cord blood culture in the diagnosis of early onset neonatal sepsis among high risk mothers

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ABSTRACT

Background: Early onset neonatal sepsis (EONS) is one of the important causes of morbidity and mortality in neonates. Its early diagnosis and prompt treatment is essential and any delay in the diagnosis can have serious consequences including neonatal death. Blood culture is the gold standard test for diagnosis of neonatal sepsis. Umbilical cord blood culture (UCBC) is a painless procedure and technically less challenging. We conducted this study to evaluate use of UCBC for the diagnosis of EONS and compared it with the results of peripheral venous blood culture (PVBC) reports. **Aims and Objectives:** The aim of the study was to evaluate UCBC for the diagnosis of EONS and compared it with the results of PVBC reports. **Materials and Methods:** This was a hospital-based prospective cohort study consisting of 100 neonates who were at risk of EONS. The study was conducted in the Department of Pediatrics Sikkim Manipal Institute of Medical Sciences Gangtok between January 2018 and December 2019. Neonates found to be at risk of development of EONS were included in this study on the basis of a predefined inclusion and exclusion criteria. Immediately after birth blood samples were collected from both umbilical cord and peripheral vein and were sent to bacteriology lab. Sensitivity, specificity, positive predictive value, and negative predictive value of both the samples were analyzed. **Results:** Out of 100 neonates in 32 (32%) EONS could be confirmed with positive sepsis screening results and/or demonstration of organisms on blood culture. Among the 32 neonates with EONS, 17 were found to be premature. The mean gestational age of newborns with EONS was found to be 35.2 weeks. The umbilical blood culture was found to have sensitivity and specificity of 100% and 74.4%, respectively, whereas peripheral vein blood culture was found to have sensitivity and specificity of 77.7% and 72.5%, respectively. The most common organism grown in our study was *Escherichia coli*. **Conclusion:** UCBC is painless and technically less challenging method of blood sampling. It has been found to have a higher sensitivity as well specificity for the diagnosis of EONS as compared to peripheral venous blood sample.

Key words: Early onset sepsis; Neonatal mortality; Umbilical cord blood culture

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INTRODUCTION

Despite the progress made by India in the past two decades in the field of medicine especially Reproductive and Child health, newborns have not gained much importance. Highest risk of dying is in the first 28 days of life. According to the WHO (2017), 46% of deaths among under five children were newborns.[1] Causes of neonatal deaths include pneumonia (16%), neonatal sepsis (12%), perinatal asphyxia (8%), and Prematurity (14%) as described by Lancet Million Death Study in 2010.[2]

Neonatal sepsis is defined in terms of early onset and late onset sepsis. EOS is usually defined as the infection occurring in first 3 days of postnatal life and is commonly caused by bacterial pathogens which are transmitted vertically from mother to neonate before or during delivery. Late-onset sepsis is defined as sepsis occurring

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usually after 72 h in NICU and up to 7 days of life in term infants and has been variably defined as occurring up to the age of <90 or 120 days. The organisms involved in late onset neonatal sepsis (LONS) is usually acquired from the environment rather than transmitted vertically from mother as seen in cases of early onset neonatal sepsis (EONS).[3]

According to National Neonatal-Perinatal Database 2002– 2003, 2219 out of 145623 (67%) neonates were found to be having EONS.[4] According to Delhi Neonatal Infection Study collaboration, total sepsis was 14.3% out of which two third cases were EONS. The organisms grown during this period were mostly Gram negative (*Acinetobacter* [22%], *Klebsiella* [17%], and *Escherichia coli* [14%]).[5] Other organisms grown were *Staphylococcus aureus*, Coagulase negative *Staphylococcus,* and *Enterococcus*. Studies have been done on various risk factors linked to development of EONS. Risk factors include prematurity, foul smelling liquor, prolonged labor, prolonged rupture of membranes for more than 1 day, more than 3 per vaginal examinations and birth asphyxia.[6] The most common presentation was respiratory distress at birth. Other clinical features include lethargy, refusal to feed, cold extremities, peripheral cyanosis, or even shock.[7] The essence of managing neonatal sepsis is early diagnosis. Even a slight delay in recognizing and managing neonatal sepsis can result in neonatal death.[8] Once the diagnosis is established appropriate antibiotics would usually be effective at least in uncomplicated cases.[9] Associated complications such as meningitis, urinary tract infection as well as metabolic disturbances including hypoglycemia needs to be appropriately managed in neonatal intensive care unit.[10] For diagnosis of neonatal sepsis blood culture is the gold standard. Collection of peripheral venous blood culture (PVBC) is difficult, involves expertise and is a painful procedure.[11] Also due to several risk factors and clinical signs, empirical antibiotics are usually started before sending blood culture due to which chances of detection of organism decreases.[12]

On the other hand, collection of umbilical cord blood culture (UCBC) is a painless procedure and technically less challenging. Moreover, it ensures adequate volume of blood for culture with less contamination and there's a possibility of yielding more positive results.[13] Therefore, we felt the need for finding the use of UCBC in the diagnosis of EONS among high risk neonates and compare it with PVBC reports.

Aims and objectives

1) To study use of umbilical cord blood culture in the diagnosis of early onset neonatal sepsis among high risk neonates.
2) To compare the results of umbilical cord blood culture with peripheral vein culture.

MATERIALS AND METHODS

This was a hospital-based prospective analytical study consisting of 100 neonates who were at risk of EONS. The study was conducted in the department of pediatrics of a tertiary care medical college situated in a semi-urban area. The neonates found to be at risk of development of EONS were included in this study on the basis of a predefined inclusion and exclusion criteria.

A neonate was considered to be a case of suspected EONS if two or more of the following risk factors were present.

A neonate was considered to be a case of suspected EONS if

(a) Two or more of the following risk factors were present.
    i) Febrile illness in mother 2 weeks before delivery.
    ii) Prematurity (<35 weeks)
    iii) Foul smelling liquor
    iv) Prolonged rupture of membranes for more than 18 h.
    v) More than 3 per vaginal examinations or single unclean examination.
    vi) Prolonged duration of first and second stage of labor for more than 24 h.
    vii) Birth asphyxia
(b) Newborns with respiratory distress since birth.
(c) Newborns born to mothers with foul smelling liquor

Confirmed case of EONS in our study was defined as newborn developing features of sepsis within 72 h of birth along with positive sepsis screening results and/or the blood culture which demonstrated growth of organism consistent with EONS.

A detailed antenatal, natal, and post-natal history was recorded in all the cases particularly those factors which may contribute toward EONS such as history of febrile illness in mother, prolonged rupture of membranes, and number of per vaginal examination was specifically asked for.

After delivery of the baby, cord was clamped and cut and baby was handed over to the pediatrician. The baby was managed till vitals were stable. Under sterile technique, the cord was wiped 3 times with 70% isopropyl alcohol and povidone-iodine. Around 1–1.5 ml of blood was withdrawn from the umbilical vein using 2 ml syringe and was injected into the aerobic culture bottle and sent for further processing to the laboratory. A sepsis screen (complete blood count, C-Reactive protein, and I: T ratio) and blood culture were performed on umbilical cord blood sample. A peripheral venous blood sample was simultaneously collected. The blood culture collected

from both umbilical cord and peripheral vein was sent to Bacteriology lab. A single group of cases was studied to avoid effect of confounding factors such as differences in gestational age or presence of different risk factors.

The analysis was done using the results of this study. One sample test and Independent sample test were used for comparison. P<0.05 was considered as being statistically significant. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated. Data analysis was done using Statistical Package for the Social Science, V26 package.

Inclusion criteria

1) The neonates born at CRH with more than or equal to 2 risk factors for early onset sepsis.
2) Newborns with respiratory distress at birth.

Exclusion criteria

1) Neonates without any risk factors or less than 2 risk factors at birth were excluded from the study.
2) Extramural newborns.
3) Neonates whose parents did not give consent.

RESULTS

Out of the 100 studied cases (suspected to be having EONS), there were 52 (52%) males and 48 (48%) females with a M: F ratio of 1: 0.92. Out of these 100 neonates in 32 (32%) EONS could be confirmed with positive sepsis screening results and/or demonstration of organisms on blood culture. Out of these 32 confirmed cases of EONS, there were 17 males (53.12 %) and 15 females (46.87%). The statistical analysis showed that the incidence of EONS was comparable in male and female neonates with no statistically significant difference in the incidence of EONS in male and female neonates (P>0.05) (Table 1).

The gestational age distribution of the newborns with suspected EONS showed that out of 100 cases majority of the neonates (64%) were full term (>37 weeks). Out of remaining 36 (36%) neonates 3 (3%) were born before 28 weeks of gestation whereas 33 (33%) neonates were born after 28 weeks but before 37 weeks of gestation. The mean gestational age was found to be 36.7±3.42 weeks. Among the 32 neonates with EONS, 17 were found to be premature. The mean gestational age of newborns with EONS was found to be 35.2 weeks.

Table 1: Gender distribution of cases

Suspected/ Confirmed EONS	Males	Females	Total
Suspected EONS	52	48	100
Confirmed EONS	17	15	32

EONS: Early onset neonatal sepsis

The distribution of cases on the basis of birth weight showed that out of 100 neonates majority (51%) had a normal birth weight (>2.5 kg) whereas out of remaining 49 cases 33 (33%) neonates had a birth weight between 1.5 and 2.5 kg. 14 (14%) and 2 (2%) neonates were very low birth weight (<1.5 kg) and extremely low birth weight (<1 kg), respectively. Among the 32 cases with confirmed EONS, 20 neonates were below 2.5 kg whereas remaining 12 neonates were having a normal birth weight (>2.5kg). Out of 32 neonates with confirmed EONS 24 (75%) were appropriate for gestational age whereas 5 (15.62%) and 3 (9.37%) neonates were small and large for gestational age, respectively. There was no statistical difference between newborns with EONS based on classification using both birth weight and gestational age as per independent samples test (P>0.05).

The analysis of the cases on the basis of mode of delivery showed that in cases with suspected EONS majority of the neonates were delivered by spontaneous vaginal delivery (48%). Cesarean section was done in 46 (46%) cases whereas instrumental vaginal delivery was done in 6 (6%) cases. In cases of confirmed EONS 16 neonates (50%) were born through spontaneous vaginal delivery whereas LSCS and instrumental vaginal delivery was done in 13 (40.62) and 3 (9.37%) cases, respectively.

The distribution of risk factors in the newborns included in our study showed that out of 100 studied cases 20 (20%) neonates had respiratory distress in immediate post-neonatal period where as history of foul smelling liquor was present in 19 (19%) cases. Out of 100 newborns with suspected EONS, 32% had positive sepsis screen and thus were confirmed EONS cases. The descriptive statistics of continuous variables of hematological tests is done for screening of suspected EONS in the newborns (Table 2).

Comparison of umbilical vein and peripheral vein blood culture results showed that out of 32 neonates with confirmed EONS 9 (9%) had positive UCBC report whereas 7 (7%) patients had a positive peripheral blood culture report. The difference in positivity of PVBC and UCBC in confirmed EONS cases was comparable with no statistically significant difference (P=0.77). Out of 93 neonates with negative peripheral vein blood culture reports 4 (%) were found to have positive UCBC report (Table 3).

The umbilical blood culture was found to have sensitivity and specificity of 100% and 74.4%, respectively, whereas

Table 2: Hematological parameters of the studied cases

Suspected/ Confirmed EONS	Parameters	Mean	Standard deviation	Range
Suspected EONS	Hb (g/dL)	17.36	2.2981	11.6–23.2
	TLC (per microL)	15262	5813.52	4130–27200
	ANC (per microL)	4088.51	3917.49	1141–19120
	Platelets (per microL)	207230	159.349	80000–354000
Confirmed EONS	Hb (g/dL)	17.34	1.996123	12–20.9
	TLC (per microL)	16952.41	6797.479	4137–27200
	ANC (per microL)	3566	5043.674	1141–191200
	Platelets (per microL)	187975	51113.858	89200–303000

EONS: Early onset neonatal sepsis

Table 3: Comparison of umbilical cord and peripheral venous blood culture

Blood Culture	UCBC				PVBC			
	Positive		Negative		Positive		Negative	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Positive	9	9	23	23	7	7	25	25
Negative	0	0	68	68	0	0	68	68
Total	9	9	91	100	7	7	93	93

UCBC: Umbilical cord blood culture, PVBC: Peripheral venous blood culture

Table 4: Sensitivity, specificity, positive, and negative predictive value of studied cases

UCBC/PVBC	Parameters	Mean
Umbilical cord blood culture in EONS	Sensitivity	100%
	Specificity	74.7%
	Positive predictive value	28.1%
	Negative predictive value	100%
Peripheral Vein Blood Culture in EONS	Sensitivity	77.7%
	Specificity	72.5%
	Positive predictive value	21.8%
	Negative predictive value	97%

EONS: Early onset neonatal sepsis

peripheral vein blood culture was found to have sensitivity and specificity of 77.7% and 72.5%, respectively. The positive and negative predictive value of umbilical cord was found to be 28.1% and 100%, respectively, whereas in cases of peripheral vein blood culture positive and negative predictive value were found to be 21.8% and 97%, respectively (Table 4).

Among cases with EONS respiratory distress was seen in 20 (20%) cases whereas history of foul smelling liquor was present in 10 (10%) cases. A combination of more than two risk factors was seen in 19 (19%) cases. A combination of two or more risk factors was present in the most common organism grown in our study was *E. coli*. There was growth of Coagulase negative staphylococcus in seven of the cultures which were found to be skin contaminants. All of the CONS were detected in PVBC. Out of five samples from newborns with EONS which detected organisms in both UCBC and PVBC, three of them had grown *E. coli,* and two of them grew *Klebsiella pneumoniae*. None of the samples grew different organism in UCBC and PVBC (Table 5).

Out of eight babies who showed positive growth on blood culture, all of them were sensitive to Amikacin, Ciprofloxacin, Colistin, Meropenem, and Piperacillin Tazobactam. Out of the three babies who had positive blood culture for Klebsiella species, 100% were sensitive to Amikacin, Colistin, and Tigecycline. About 50% were sensitive to Piperacillin Tazobactam. 45% were sensitive to Ciprofloxacin. 100% were resistant to Ampicillin, Cefepime, Cefoperazone, and Ciprofloxacin. Only one had detected *Pseudomonas* growth which was sensitive to only Colistin (100%). Tigecycline was 50% and Amikacin was 45% sensitive to *Pseudomonas*.

Out of 100 patients suspected to be having EONS 88 (88%) improved whereas seven neonates expired and five neonates were lost to follow-up (shifted to other hospitals or discharged against medical advice). Among 32 neonates with suspected EONS 27 (84.37%) improved, 4 (12.5%) expired, and 1 (3.12) neonate was lost to follow-up (Figure 1).

DISCUSSION

In our study, out of 2182 live births, 32 newborns had clinical and laboratory features of EONS. The occurrence of EONS in our study is approximately 1.5%. A prospective study done in tertiary care center reported an incidence of 9.8% of total live births.[14] The occurrence of EONS in our study was lower from the above study as our study

Table 5: Organisms isolated in umbilical as well as peripheral vein blood cultures

Organism	UCBC		PVBC	
	Frequency	Percentage	Frequency	Percentage
Escherichia coli	6	6	4	4
Klebsiella pneumoniae	3	3	2	2
Pseudomonas	0	0	1	1
Sterile (No Growth)	91	91	93	93
Total	100	100	100	100

UCBC: Umbilical cord blood culture, PVBC: Peripheral venous blood culture

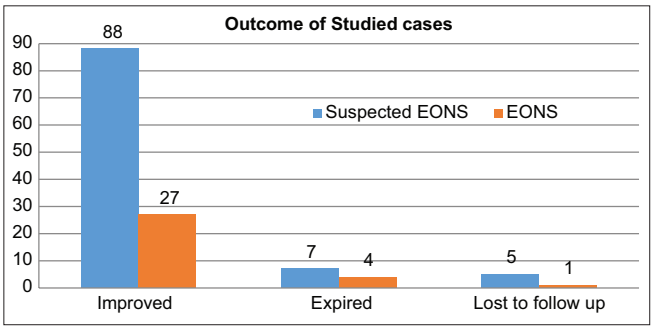

Figure 1: Outcome of neonates with early onset neonatal sepsis

data are from single tertiary center and only in-borns were included in the study. The other authors such as Randis et al.,[15] reported the incidence of neonatal sepsis to be a bit higher, that is, 6.6%.

In the present study, out of 100 neonates with suspected EONS, 52% were males whereas out of the 32 neonates with EONS, 53% are males. There is no statistical difference between male and female newborns for the occurrence of EONS. The male to female ratio of newborns with suspected EONS will vary according to the sex ratio of the region in which the study is being done. During the study period, it was observed that 50.6% of the babies born in our hospital were males.

In our study, 64 term neonates and 36 preterm neonates were screened for sepsis, out of which 17 (53%) were preterm and 15 (47%) were term who developed EONS. Our observations are consistent with most of the studies showing a higher occurrence of EONS in preterm despite more term babies being screened for sepsis. These findings are explained by the association of spontaneous prematurity with maternal genital infections as well as relative immunocompromised state of preterm neonates which makes them vulnerable for developing sepsis on exposure to infections. An observational cohort study done on early and late onset sepsis in late preterm infants by Cohen-Wolkowiez et al., concluded that late preterm infants demonstrate specific infection rates, pathogen distribution and mortality associated with EONS and LONS.[16] 59% of the neonates screened for EONS were low birth weight and 62% of the neonates with EONS were low birth weight.

A study done by Sobaih and Al-Mandeel on early and LONS in very low birth weight infants in a tertiary Center in Saudi Arabia involved babies weighing 500–1500 g over a 9 year period in which incidence of EONS was 10.9%.[17] Another study done by Hornik et al., on Early and Late Onset Sepsis in very low birth weight infants from a large group of NICU involved 108000 VLBW infants out of which EONS occurred in 1032 infants.[18] The higher occurrence of neonatal sepsis in low birth weight babies may be due to poor immunological status of the newborns.

In our study, the risk factors considered for development of EONS is elaborated in materials and methods. The presence of foul smelling liquor or two or more of the risk factors as mentioned is considered as inclusion criteria for the newborns in our study. These risk factors are based on studies from India with a high impact, validity and reliability. In our study, 70% of the neonates had more than 2 risk factors for the development of EONS and 60% of the newborns with EONS had more than 2 risk factors. These findings are similar to studies on utility of cord blood cultures in EONS by Meena et al., where the risk factor distribution with suspected EONS and EONS were common in both groups.[19] A study by Rathi in a tertiary care neonatal unit of a reputed medical college, 13% of the newborns with EONS had presence of foul smelling liquor similar to our studies. As per most studies on EONS, the most common presentation of EONS is reported as development of respiratory distress since birth.[20]

32 out of 100 neonates screened for sepsis had sepsis screening results positive and 85% newborns with positive sepsis screen results had clinical features of EONS. Aundhakar et al., had done a study of UCBC in the diagnosis of EONS among newborns with high risk factors at a tertiary care neonatal intensive care unit in which 24 out of 75 (32%) had sepsis screen positive.[21] Mandot and Gandhi had done a similar study which revealed that 23 babies out of 80 (30.6%) had positive sepsis screening.[22]

In our study, 9% of the UCBC from newborns with suspected EONS had significant growth of organism consistent with EONS as compared to 7% by PVBC. About 5% of the newborns with suspected EONS had

both UCBC and PVBC positive. The sensitivity of UCBC in our study was 100% and specificity 74.7%. The sensitivity of PVBC in our study was 77.7% and specificity was 72.5%. In our study, the most common organism grown was *E. coli,* followed by *K. pneumoniae* and *Pseudomonas*. Seven of the cultures detected CONS which were confirmed as skin contaminants both clinically and bacteriologically. All of them were isolated from PVBC. None of the UCBC revealed organisms which were contaminants. In our study, there was no growth of Gram-positive organisms in both UCBC and PVBC. The organisms responsible for EONS as per various Indian data for EONS are as follows. In a study done by Bhat et al., on 2182 neonates, *Pseudomonas* (33.2%) was the most common organism, followed by *Klebsiella* (31.4%), *Acinetobacter* (14.4%), *S. aureus* (9.2%), *E. coli* (4.4%), *Citrobacter* (3.05%), and Enterobacter (2.2%).[23] Chacko and Sohi did a study on EONS in which 136 neonates with risk factors for EONS and the most common organism isolated was *Pseudomonas* (60%).[24] Tallur et al., reported Klebsiella and *Pseudomonas* to be the most common organisms causing EONS.[25]

Limitations of the study

The limitation of this study was small number of cases. Similar studies with large number of cases and an independent comparator group will be required to further substantiate the results of this study.

CONCLUSION

UCBC is a convenient method for collection of blood sample in immediate post neonatal period. It ensures painless collection of blood samples in adequate volumes which sometimes is difficult particularly in preterm neonates. One of the distinct advantages with UCBC is very low incidence of contaminant growth in blood culture which is a common occurrence in cases of peripheral vein blood samples.

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An audit of MTP in women with high-risk pregnancy

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ABSTRACT

Background: The women who have been pregnant more than four times are fewer than 18or over 35-years-old, or have at least one medical issue before or during pregnancy, the pregnancy is considered high-risk. Increased maternal and foetal mortality and morbidity are linked to these risk factors. MTP in itself is a blind and risky procedure and performing it in High Risk Pregnancy (HRP) is a challenge for obstetrics and gynecology personnel. When performed with all pre, intra and post-op precautions, results are good and patient-friendly. **Aims and Objectives:** Aims of the study were to calculate the number, high-risk factors, method used, and its outcome of MTP in HRP. **Materials and Methods:** The present study was a retrospective observational study done at QMH, KGMU, Lucknow performed on subjects admitted for MTP from January 2018 to December 2018. Total admitted patients seeking MTP were 450 out of which 93 belonged to High-Risk Group who underwent surgical and medical abortion accordingly. All precautions and norms defined by Govt. of India were taken care of. Cases were evaluated on the basis of high-risk factors- Age, parity, obstetrical and medical illnesses, and interval since last delivery. **Results:** Out of 93 high-risk cases, 88 cases were of 1st trimester and 5 were of 2nd trimester abortion. Six cases required suction evacuation while seven cases were managed medically using medical abortion kit. Contraception was given to all subjects according to their needs. Seventy-one women were of more than 35 yrs, while two were teenagers. 21 women were grand multipara. Women of obstetrical risk were 17 while the rest were having medical illnesses. **Conclusion:** This study concludes that there are a large number of high-risk groups for MTP again showing unmet need and lack of specialized counseling of HR patients according to their mental and physical condition. Early recognition of pregnancy and timely intervention can be lifesaving in these women and proper contraceptive counseling is required to prevent future pregnancies.

Key words: Abortion; Contraceptions; Foetal mortality; High-risk pregnancies; MTP

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INTRODUCTION

If the women have been pregnant more than 4 times, are fewer than 18 or over 35-years-old, or has at least one medical issue before or during pregnancy, the pregnancy is considered high-risk. Increased maternal and fetal mortality and morbidity are linked to these risk factors.[1] Prenatal and postpartum care, contraception, and abortion are all essential reproductive health interventions for women at high risk of maternal morbidity and mortality. However, obstacles such as restrictive state law and a lack of qualified providers must be overcome.[2]

According to the World Health Organization (WHO), 830 women die every day as a result of problems during pregnancy or childbirth. High-risk pregnancy (HRP) is more common in some countries.[3]

The nationwide rate for unmet need, according to the National Family Health Survey-3 (NFHS-3) 3, is 13%. According to the District Level Household and Facility Survey-3 (DLHS-3) 4, India has a 21.3% unmet

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contraceptive requirement, with 7.9% for spacing and 13.4% for limiting.[4] NFHS-4 stated high unmet need for Family planning among married women in U.P.[5]

High-risk mothers contribute for 70–80% of perinatal death and morbidity, despite accounting for just 10–30% of all mothers examined during the antenatal period.[6] Nearly 529000 women die every year in the world as a result of pregnancy-related conditions. Nearly 118 women are killed or suffer severe acute morbidity for every death.[7] Early identification and very intensive treatment for high-risk pregnancies can have a major impact on perinatal outcomes. As a result, all pregnancies should be assessed to see whether or not risk factors exist or will exist.[8] Age, parity, and social status are all factors to consider. Mothers with a history of chronic disease (diabetes, hypertension, heart disease, etc.) or past pregnancy issues (abortion and stillbirth) as well as multiple pregnancies, gestational age under 18 or over 35 years, and pregnancy more than four times are all factors to consider when calculating the risk of any pregnant woman.[9] HRP may cause prenatal problems (e.g., fetal death) in addition to maternal death. 1 Despite the evident need for improved care and awareness of the hazards, some women chose to become pregnant on their own volition. They remained determined to do so, employing numerous techniques to boost their chances of becoming pregnant and hoping for a healthy kid. Pregnant women may take efforts to protect their own and their fetuses' health, but this does not always imply that they are following medical advice.[10] Several studies have looked at the effects of mother education on pregnancy difficulties and the risk factors that go along with them.[11-13]

MTP or abortion laws have been liberalized over the world during the past few decades. Abortion has been legal in India since 1972 to lessen the maternal morbidity and death associated with illicit abortions.[14] It is necessary to promote the use of contraceptive techniques in order to reduce the number of abortions, some of which are high-risk and dangerous. Most countries have moderate to high abortion rates, owing to poorer contraceptive use prevalence and efficacy.[15] Unfortunately, abortion has become a popular means of restricting and spacing births, but it should never be advocated as a means of family planning.[16]

Between 2015 and 2019, 73.3 million induced (safe and unsafe) abortions were performed annually on a global scale.[17] Induced abortions were reported to be 39/1000 women aged 15–49. Induced abortions occurred in 3 out of 10 (29%) of all pregnancies and 6 out of 10 (61%) of all unwanted pregnancies.[17]

A high risk pregnancies have a high adverse maternal fetal outcome scoring system was proposed by Coopland *et al.*,[18] HRP includes the following factors such as - Age at delivery <19, >30 yrs, grand multipara, heart disease, hypertension disorder, ch HT, anemia, rheumatic heart disease (RHD), diabetes mellitus (DM), HIV, AIDS malignancies, previous Cesarean Section, multiple pregnancies, and congenital uterine malformation.[18]

According to the WHO any woman who is pregnant and cannot have a safe abortion is at risk or complications of having an unsafe abortion may suffer a variety of consequences that affect their quality of life and well-being, with some facing life-threatening problems. Hemorrhage, infection, and harm to the vaginal tract and internal organs are the most serious life-threatening complications associated with the least safe abortions.[3] Despite the fact that many studies have been conducted to assess the prevalence of HRP in India, there have been fewer studies conducted to establish the outcomes of HRP in different parts of India.[19] In our present study, we included the study of MTP on HRP is done by supervised and skilled personnel.

Aims and objectives

Aim of the study was intended to calculate the number of women with HRP undergoing MTP, to study the risk factors involved in these women, to study the method used for termination of pregnancy and to study the end result after the procedure and safety of MTP in high-risk pregnancies. Both the methods of MTP surgical and medical have been used for the patients in this study. MTP in various high risk factors has been observed for various parameters.

MATERIALS AND METHODS

The present observational study was done in the Department of Obstetrics and Gynaecology King George's Medical College, Lucknow UP, India, from the study period from Jan 2018 to Dec 2018. Total admitted patients seeking MTP were 450 out of which 93 participants were enrolled in this study after taking written informed consent form, in the number of MTP's done during this period; women were identified for high-risk factors present. Termination of pregnancy was done after proper consent and as per GOI guidelines either surgical/medical. Out of 93 HRP for termination 88 were first-trimester abortion and 5 cases were of 2nd trimester abortion. MTP of the entire participant was terminated by medical and surgical method, seven cases were terminated by medical method, and 86 cases were done by surgical method.

Medical method

Mifestrone 200 mg F/B misoprostol 400 mg BD given after up to 48 9 (Sublingual), Mifesterone 200 mg followed by

misoprostol 200 mg 4 mg after 48 h in second trimester (Per vaginal).

Surgical method

Section evacuation done 4 m sedation and local anesthesia and followed by per vaginal misoprostol given per vaginal for 2 weeks prior to surgery.

Inclusion and exclusion criteria

All patients who fulfill indications of MTP and <20 weeks of pregnancy were included in study cases unwilling to sign informed consent were excluded from the study.

Investigations and data collection

Records of PP unit of QMH from Jan 2018 to Dec 2018 were utilized to provide data for this observational study. Subjects were investigated for Hemoglobin, Viral Marker, Blood group (ABO and RH), blotting time, clotting time, and Ultrasound done according to need for relevant medical illnesses as required.

Statistical analysis

For continuous data, normality was tested using the Kolmogorov Smirnov test. For non-normal continuous data, the Kruskal Wallis H test was used to compare the groups as appropriate. Categorical data were presented in frequency and percentage. Statistical analysis was carried out using the statistical package for social science, version 22 (SPSS-22, IBM, Chicago, USA). Two-tailed P<0.05 has been considered as statistically significant.

RESULTS

In this present study, Table 1 showing that the majority of women (76.344%) pregnant were age of 35 years and above, 13.979% were 30–34 years, 2.150% were teenagers pregnancy, 60.439% women were multipapa (were 37.634% having two children and 21.506% having three child), 22.580% women were grand multipara (4 or more). Table 1 also shows that interval MTP since last delivery were the majority (32.258%)of women having 2–5 years and less women (15.053%) were less than and equal to 1 year.

Distribution of women according to obstetrics and medical risk factor (Table 2) 71% women having age 35 years or above, 58% were multipara, 21% women were grand multipara, 17 women (18.279%) previous lower segment caesarian section (LSCS) and 10 (10.752%) RHD and 4 (4.301%) malignancy and Diabetes Mellitus respectively, 1 (1.075) women were and chronic kidney disease, CVA, chronic liver diseases and hypertension respectively, i.e., medical disorder contributed 18.279% in this study.

Contraceptive acceptance by women undergoes MTP was given in Table 3 40% of women accepted IUCD, 30% underwent sterilization, 1.075% of women had chosen barrier method for contraception, OCP's, and injectable contraception, rest had not taken any contraception after MTP (Table 3).

Complications of HRP after MTP were shown in Figure 1, 79.569% of women has no complications after MTP, 12.903% of women had mild and moderate pain in the abdomen,5.376% of women has vaginal bleeding complain and less approximately 2.150% of women has complained of nausea and vomiting.

Table 1: Demographic distribution of high-risk factors

Parameters	Risk factor	Number of women (n=93)	Percentage
Age	<19 years	2	2.150
	20–24 years	3	3.225
	25–29 years	4	4.301
	30–34 years	13	13.979
	35 yrs or above	71	76.344
Parity	P0	5	5.376
	P1	12	12.903
	P2	35	37.634
	P3	20	21.505
	P4 or more	21	22.580
Interval since last delivery	≤1 year	13	13.978
	2–5 years	30	33.333
	5–9 years	28	22.580
	≥10 years	22	23.655

Table 2: Distribution of high risk pregnancies by high risk of obstetrical and medical factors

Risk factors	Number of women	Percentage
Age>35 years	71	61.290
Multipara	55	54.838
Grand multipara	21	22.580
RHD	5	5.376
Previous LSCS	17	18.279
Chronic kidney disease	1	1.075
Malignancy	4	4.301
CVA	1	1.075
Chronic liver disease	1	1.075
Diabetes mellitus	4	4.301
Hypertension	1	1.075

Table 3: Distribution of method of contraception post MTP

Method of contraception	Number of women	Percentage
None	20	21.505
Barrier contraceptives	1	1.075
OCP's	1	1.075
Injectable contraceptives	1	1.075
Copper T	40	43.010
Lap ligation	30	32.259

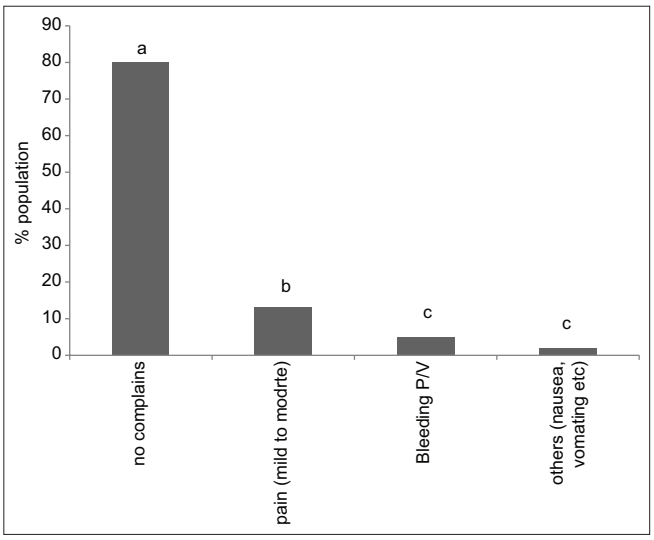

Figure 1: Complications of high risk pregnancy after MTP; different alphabets shows significant variation between groups; Kruskal-Wallis H test was used to calculate significance level at P<0.05

DISCUSSION

This study basically involved the women belonging to high risk pregnant females in reproductive age group seeking MTP for various indications falling in to guidelines laid by GOI which includes the continuation of pregnancy that would involve a risk to the life of pregnant women or of grave injury to her physical or mental health.

Results show that incidence of HRP for MTP in our hospital group is about 20.6 and they all need extra measures and care during and after MTP because of their risk factors like they require extra check-up and supervision for antenatal and post-natal period.

Amongst all risk factors, Maximum number 76.344% women were of elderly age group, 35 years or more. Next to this 37.634% of women having two kids reflected the large unmet need of contraception in our study. Patients with medical disorders contributed to 18.279%.This shows that there are still large unmet needs of contraception. In another study conducted in Egypt, the majority of the participants (44%) were between the ages of 30 to 35 years.[7] HRP includes following factors like – Age at delivery <19, >30 yrs, Grand multipara, Heart disease, hypertension disorder, ch HT, anemia, RHD, DM, HIV, AIDS malignancies, previous Cesarean Section, multiple pregnancies, and congenital uterine malformation.[18] In a previous study the prevalence of HRP was higher i.e., 77% in multigravida compared to primigravida (23%).[20] Our present study shows higher multiparous (53.838%) as compared to primiparous (12.903%). Previous study also shows higher multiparous as compared to primiparous. HRP was found to be linked to parity and socioeconomic status independently In a research conducted in Karnataka, similar results were found.[21] Another study in Rohtak, Haryana, India, revealed that 13.7% of grand multigravida (four and above) women had high risk.[8]

Patients with medical disorders like RHD, chronic heart disease malignancy, CVA, chronic liver disease, DM and hypertension contributed to 18.682% in this study. High blood pressure, gestational diabetes, and delivery difficulties are all more common in women over 35.[22] When a woman has experienced a difficulty during one pregnancy, such as preterm birth, a baby with birth abnormalities, previous abortion, past stillbirth, or a previous caesarean section, she is more likely to experience the same problem with subsequent pregnancies.[23-26] Hypertension was found in 22% of high-risk pregnancies, according to a previous study.[8] A previous study done in Nagpur also revealed that HRP had significant association with LSCS, which is contrast to our current study 18.279% women were previous LSCS.[19]

A large number of women had a long inter delivery interval. In this study, number of 30.107% women had 5–9 years of interval since their last delivery. 23.655% were 10 years and above. Patients of these groups require extra care and precautions advised from specialists so complications and post procedure problems were minimal because of these measures taken all the patients were given contraception according to their need and health issues. NFHS-4 stated high unmet need for Family planning among married women in U.P. Unmet needs are found quite high in my studies also. Total unmet need has 12.1 and for spacing has 5.1,[5] which could not be calculated in our study because we have taken patients with contraceptive failure and only high risk groups. Previously there was a 27.3% unmet need for contraceptives. There was a 4.9% and 22.5% unmet requirement for spacing and restricting, respectively. Client-related reasons were cited by 50% of those with unmet need (n=73), while contraception-related factors were cited by 37% (availability, accessibility, affordability, side effects).[27]

Limitations of the study

We were unable to collect information on a variety of potential risk variables for HRP, including education, employment status, spousal support, age at marriage, and age at first pregnancy. Due to the inability to extract data on time of exposure from case records, causal results for factors connected to HRP and outcomes cannot be deduced. More studies need to be done to focus on factors that influence HRP and pregnancy outcomes.

CONCLUSION

We concluded that the major cause of HRP is related to maternal age and multipara with. Similarly pregnancy with

RHD, chronic kidney disease, previous LSCS, malignancies, D.M, other medical disorders has serious fetoe-maternal outcomes so if indicated safe abortions are life saving for these women and they can help in reducing maternal mortality as well as in decreasing Infant mortality rate. A large number of high-risk groups for MTP again showing the unmet need and lack of specialized counseling of HR patients according to their mental and physical condition. Early recognition of pregnancy and timely intervention can be lifesaving in these women and proper contraceptive counseling is required to prevent future pregnancies. This present study is showing the only tip of the iceberg of the problem. A lot more awareness is required and postnatal contraception is a must. MTP is a nightmare in some medical disorders and they are being refused at early pregnancy when it is safer than performing in late or advanced pregnancy or if they continue the pregnancy. So providing them safe supervised abortion services to be considered over just refusing safe abortion services merely because of high risk factors.

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Review of PPIUCD at tertiary care centre in Southern Rajasthan

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ABSTRACT

Background: This study was conducted to observe the acceptance rate and safety for PPIUCD as PPIUCD was used as contraceptive method under family welfare program in this institute. **Aims and Objectives:** To see pattern of acceptance and safety of PPIUCD among women admitted for childbirth. **Materials and Methods:** A prospective, preformed semi-structured questionnaire-based observational study was conducted between September 2012 and August 2020 in the Government Medical College Kota. CuT380A was used as PPIUCD for insertion. WHO medical eligibility criteria were met along with inclusion and exclusion criteria. After counseling and consent, PPIUCD was inserted post-placentaly and during LSCS. Acceptance rate was calculated along with safety profile. **Results:** In the present study majority of patients were in the age group of 21–30 years. 44.26% women were second para. 96.35% insertions were uneventful during the study. The most common reason for acceptance and refusal of PPIUCD was reversibility and for refusal was fear of complications, respectively. The acceptance was increasing over the years. On follow-up majority of clients had no complaints. Among those who had complaints, irregular bleeding was most common. Major cause of requesting for removal was irregular bleeding. Continuation rate was found to be 91.91% and 85.30% at 6 weeks and 6 months, respectively. **Conclusion:** PPIUCD is a safe and effective method of contraception. Acceptance rate is increasing over the years and which can further increase with antenatal, intra natal and postnatal counseling along with counseling of husband/family attendants and management of side effects.

Key words: Acceptance; CuT380A; Intra-caesarean insertion; Postpartum insertion; Postpartum intrauterine contraceptive device; Safety

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INTRODUCTION

According to the 2005–2006 National Family Health Survey, 61% of births in India were spaced <3 years and that 22% of married women had an unmet need for family planning.[1] A stratified analysis suggested that 65% of women in the 1st year postpartum had an unmet need for family planning.[2] Only 26% of women are using any method of family planning during the 1st year postpartum.[3]

Over the years with the introduction of IUCD in family welfare program in India awareness and opportunity to get a long-term reversible contraceptive in form of IUCD during postpartum period is increasing day by day to all childbearing women as institutional deliveries also increasing regularly due to introduction of JSY and JSSK.

Aims and objectives

1. To see pattern in acceptance of PPIUCD among women admitted for childbirth.
2. To assess the safety of PPIUCD.

MATERIALS AND METHODS

A prospective, preformed semi-structured questionnaire-based observational study was conducted between September 2012 and August 2020 in the Department of Obstetrics and Gynaecology, Government Medical College Kota, Rajasthan.

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In family welfare program PPIUCD (CuT380A) was used in this institute. After applying inclusion and exclusion criteria contraceptive counselling was given to all women irrespective of gestational age, maternal age, other risk factors such as parity and proposed mode of delivery presenting in antenatal clinic and to all labor room admissions for delivery. To calculate acceptance, all counseled women admitted for delivery were included in the study. Those who gave written consent for PPIUCD received an intrauterine contraceptive device within 48 h of placental expulsion in normal deliveries and post placental in caesarean deliveries. All four WHO Medical Eligibility criteria were met in the study.[4]

Inclusion criteria

All women admitted for childbirth in our institute were counselled for PPIUCD. Consent was obtained from those, who opted for insertion. The following criteria were considered for inclusion in the present study.

1. 18–45-years-old.
2. Desire to have IUCD after counselling.
3. No local infections.
4. Hb>10 gm%.

Those women who fulfilled the criteria for insertion were given PPIUCD irrespective of the mode of delivery.

Those women who had either of the following were **excluded** from the study:

1. Patient with Haemoglobin <8 g/L.
2. Un-booked cases handled by Dais.
3. Temperature >38°C or more after labour/ Chorioamnionitis
4. Rupture of membranes >18 h prior to labor
5. Un resolved Post-partum haemorrhage

Follow-up was scheduled at 6 weeks and 6th month after insertion.

Each client was asked regarding her experience during the past 6 weeks and 6 months. Their complaints were noted and they were examined regarding thread *in situ*, infection, evidence of partial expulsion, missing thread etc. USG was done if the thread was not seen and there was no history of expulsion. All cases in which woman gave history of expulsion were also subjected to USG for confirmation.

Those who had complaints such as irregular bleeding and pain abdomen without evidence of infection and IUCD in correct position were given symptomatic treatment and counselled to assure willingness to continue the IUCD. Those who wanted removal on these ground IUCD was removed. Those who had no complaints; and on examination the IUCD was in place were given reassurance and advised to come for the next follow-up.

Those who did not come for scheduled follow up were phoned up. Some of them came late and some were lost to follow up.

Safety was assessed on basis of patient's complaints with respect to excess bleeding, pain abdomen, abnormal discharge if any. Complications such as perforation (if any) were noted. Expulsion rates at 6 weeks and 6 months follow-up were measured.

Software SPSS ver. 16 and Microsoft Excel will be used for statistical analysis.

RESULTS

In the present study majority (85.14%) of patients were in the age group of 21–30 years followed by 10.25% in <20 years age group. Most (75.23%) of women included in the study were literate up to 12 classes followed by 14.75% of illiterate participants. In the present study, 81.96% of women were Hindu followed by 15.50% Muslim women (Table 1).

In the present study, 44.26% of women were second para followed by 31.25% primiparous women. About 50.83% insertions were made in post-placental period followed

Table 1: Demographic profile of clients

Demographic character	Insertions n (%)
Age	
<20 years	883 (10.25)
21–30 years	7331 (85.14)
31–40 years	397 (4.81)
Education	
Illiterate	1270 (14.75)
<12th standard	6478 (75.23)
>12th standard	863 (10.02)
Religion	
Hindu	7058 (81.96)
Muslim	1335 (15.50)
Others	218 (2.53)

Table 2: Parity, time of insertion and event after insertion

Character	n (%)
Parity	
Primiparous	2691 (31.25)
Second Para	3828 (44.26)
Multi parous	2092 (24.29)
Time of Insertion	
Post-placental	4377 (50.83)
Post-partum with in 48 hours	665 (7.72)
Intra-caesarean	3569 (41.45)
Events in Immediate postpartum period	
Uneventful	8237 (96.35)
Post-partum haemorrhage	288 (3.34)
Removal of IUCD	26 (0.3)
Perforation	00 (00)

by 41.45% during LSCS. About 96.35% insertions were uneventful during the study (Table 2).

Most common (25.95%) reason for acceptance of PPIUCD was reversibility of method followed by long term use of IUCD (23.93%).

Major reason (31%) for refusal was fear of complications followed by husband/family refusal (25.99%) (Table 3).

After applying inclusion and exclusion criteria out of 124234 deliveries in study duration only 44606 women could get counselled about PPIUCD. From these counseled women 8611 women accepted PPIUCD so cumulative acceptance rate among counseled women was 19.30% (Table 4).

As awareness and information and antenatal counselling were increasing on PPIUCD the acceptance was also increasing for PPIUCD as it was 9.10% of total counselled deliveries in 2012 and raised to 34.68% in 2020 (Table 5).

Table 3: Reason for acceptance and refusal

Reason	n (%)
Reason for acceptance	
Reversible	2242 (25.95)
Long term	2061 (23.93)
No remembrance once inserted	1639 (19.01)
Fewer clinic visit	1376 (15.98)
Safe	602 (6.99)
Faith on doctor	517 (6.00)
No interference with breastfeeding	174 (2.02)
Reason for refusal	
Fear of complications	11159 (31)
Husband/family Refusal	9351 (25.99)
Prefer other contraceptive method	6119 (6.99)
Wants permanent method	2521 (7.00)
Myth that she does not want any contraceptive method	1820 (5.05)

Table 4: Acceptance of PPIUCD

Total number of counselled	44606
Accepted	8611 (19.30)
Refusal	35995 (80.70)

On follow up at 6 weeks and 6 months majority (86.11% and 87.68%) of clients were having no complaints. Among those who had complaints, irregular bleeding was most common (5.64% and 3.07%) followed by pain abdomen (3.50% and 2.45%).

Study had 2.00% and 1.22% of clients as lost to follow-up at 6 weeks and 6 months, respectively. So at 6 weeks, 173 were lost to follow-up and 523 removal were excluded from the further part of the study (Table 6).

About 92.86% and 92.44% of clients had their thread *in situ* on examination at 6 weeks and 6 months, respectively. Only 3.24% and 2.47% clients had missing thread on examination during follow up at 6 weeks and 6 months, respectively.

About 06.19% and 5.84% clients requested removal on follow up at 6 weeks and 6 months, respectively. Major cause of requesting for removal was irregular bleeding in 39.57% and 26.78% followed by pain abdomen in 17.01% and 14.25% during follow-up at 6 weeks and 6 months, respectively (Table 7).

The study found continuation rate of 91.91% and 85.30% at 6 weeks and 6 months, respectively along with zero perforation (Table 8).

DISCUSSION

Present study found that majority of acceptors were in the age group of 21–30 years which is in accordance to various prior studies.[5-8]

Most (75.23%) of women participated in the present study were literate up to 12th standard while study done by Jain and Bindal,[5] Gnanasekar[7] and Gonie et al.,[8] found that majority of acceptors had primary level, graduate level and secondary level of education, respectively.

In the present study, 81.96% of women were Hindu followed by 15.50% Muslim women. In the present study,

Table 5: Number of counselled and insertions (Year wise)

Year	Total Deliveries	Total Counselled (%)	Counselled in ND (%)	Counselled in LSCS (%)	Insertions in ND (%)	Insertions in LSCS (%)	Total Insertions (%)
2012	10329	1998 (19.34)	1102 (55.16)	896 (44.86)	117 (10.61)	65 (7.25)	182 (9.10)
2013	11805	2056 (17.41)	1212 (58.94)	844 (41.06)	199 (16.41)	143 (16.94)	342 (16.63)
2014	13128	4002 (30.48)	2818 (70.14)	1184 (29.56)	217 (7.70)	195 (16.46)	412 (10.29)
2015	14642	4786 (32.68)	3315 (69.26)	1471 (30.74)	321 (9.68)	332 (22.56)	653 (13.64)
2016	15850	5402 (34.08)	3856 (71.38)	1546 (28.62)	409 (10.60)	521 (33.69)	930 (17.21)
2017	16327	6232 (38.16)	4123 (66.15)	2109 (33.85)	455 (11.03)	499 (23.66)	1054 (16.91)
2018	15770	7296 (46.26)	4945 (67.77)	2351 (31.72)	440 (8.89)	696 (29.60)	1136 (15.57)
2019	15565	7967 (51.18)	5452 (68.43)	2515 (31.57)	1286 (23.58)	952 (37.85)	2238 (28.09)
2020	10818	4867 (44.98)	3125 (64.20)	1742 (35.80)	656 (20.99)	1008 (57.86)	1664 (34.18)

Table 6: Follow up complaints and lost to follow up

Follow up complaints	6th week	6th month
No complaints	7266 (86.11)	6940 (87.68)
Irregular Bleeding	476 (5.64)	243 (3.07)
Pain Abdomen	296 (3.50)	194 (2.45)
White Discahrge	53 (0.62)	35 (0.44)
Expulsion	26 (0.30)	13 (0.16)
Others	125 (1.48)	97 (1.22)
Lost to follow up	173 (2.00)	106 (1.33)

Table 7: Finding and removal of iucd on follow up and cause of removal

Finding on follow up and cause of removal	6th week	6th month
Finding on follow-up examination		
Thread *in situ*	7836 (92.86)	7317 (92.44)
Partial expulsion	132 (1.56)	9 (0.11)
Missing string	274 (3.24)	196 (2.47)
Removal of IUCD	523 (6.19)	463 (5.84)
Cause of removal		
Irregular bleeding	207 (39.57)	124 (26.78)
Pain abdomen	89 (17.01)	66 (14.25)
Partial expulsion	132 (25.23)	9 (1.94)
Social	67 (12.81)	39 (8.42)
Others	28 (5.35)	35 (7.55)

Table 8: Continuation Rate for PPIUCD

Continuation rate	6th week	6th month
Continuation rate	7915 (91.91)	7346 (85.30)

44.26% of women were second para which was similar to study conducted by Gonie et al.,[8] Studies conducted by Jain and Bindal,[5] Madhuri and Sreelakshmi[6] and Gnanasekar[7] had more primiparous as most common acceptor.

In this study 50.83% insertions were made in post-placental period followed by 41.45% during LSCS which is similar to another study conducted by Ranjana et al.,[9] which had 52.94% post-placental 42.64% intra caesarean and 4.41% post-partum insertion. While in study by Vilvapriya and Veeraragavan[10] 78.3% of insertions were intra Caesarean 14% post-placental and 7.7% were postpartum.

About 96.35% insertions were uneventful during the study which was similar to study done by Agarwal and Singh.[11]

The present study revealed that the most common (25.95%) reason for acceptance of PPIUCD was reversibility of this method while study conducted by Jain and Bindal et al.,[5] and Gnanasekar[7] found non-hormonal property and non-interference to breastfeeding property of PPIUCD as most common reason for acceptance respectively. In a study done by Barala et al.,[12] long life of PPIUCD was most common reason for choosing this method of contraception.

This study found fear of complications as major reason (31%) for refusal of PPIUCD which was similar to study done by Jain and Bindal et al.,[5] and Gnanasekar[7] while Barala et al.,[12] revealed the use of another method of contraception as common cause of refusal of this method.

This study found cumulative acceptance rate of 19.30% which is comparable to Gnanasekar[7], Gonie et al.,[8] and Barala et al.[12]

The present study found that during the study period the acceptance rate was continuously increasing year wise. This may be due to raising level of awareness knowledge and regular antenatal counselling for contraception. No other study calculated yearly acceptance rate so far.

In our study on follow-up at 6 weeks and 6 months majority of clients were having no complaints. This is comparable to study findings of Agarwal and Singh[11] and Chauhan et al.,[13] while Jain et al.,[14] found clients without complaints were only 24.75% and 19.25%.

Among those who had complaints, irregular bleeding and pain abdomen were most common. This finding was similar to previous studies.[5,6,11,15]

The study had 1.48% and 1.22% of clients as lost to follow-up at 6 weeks and 6 months respectively which is less than other studies.[7,16]

More than 90% of clients had their thread *in situ* on examination on follow up which is comparable to finding of Gnanasekar[7] and Agarwal and Singh.[11]

This study revealed that 3.24% and 2.47% of clients had missing thread on examination on follow up which is similar to the study conducted by Pandher et al.,[15] while other studies had more missing threads present study.[6,7,11]

About 6% of clients requested IUCD removal on follow up which was less than study done by Gnanasekar[7], Ranjana et al.,[9] and Rani et al.[17]

Major causes of requesting for removal were irregular bleeding and pain abdomen on follow up which were similar to studies done by Madhuri and Sreelakshmi[6], Gnanasekar[7] and Ranjana et al.[9]

Study found continuation rate of 91.91% and 85.30% on follow-up which is comparable to findings revealed in studies done by Madhuri and Sreelakshmi[6] and Pandher et al.[15]

Limitations of the study

Number of counselors were inadequate during initial part of study period and Lost to follow up clients could not be traced because of limited resources.

CONCLUSION

PPIUCD is safe and effective method of contraception. Over the years acceptance rate for PPIUCD was increased which can further increase with antenatal, intra natal and postnatal counselling along with counselling of husband/family attendants and management of side effects acceptance rate can be improved. In developing countries where postnatal services including contraception are not frequently utilised by mothers/families, it can be an effective tool to slow down population growth.

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A comparative study on echocardiographic evaluation of the left ventricular mass and function in normotensive diabetic and non-diabetic patient

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ABSTRACT

Background: Cardiovascular complications account for the highest mortality in diabetic patients, mainly due to coronary artery disease and congestive heart failure. Left ventricular hypertrophy (LVH) is an ominous prognostic sign and an independent risk factor for cardiac events which is frequently present in patients living with diabetes. **Aims and Objectives:** The aim of the study was to evaluate the LV mass and function in normotensive diabetes patients without antihypertensive medication. **Materials and Methods:** 100 normotensive diabetic patients were in study group and 100 control patients were studied. Hypertension and other known causes of LVH were excluded from the study. Data were analyzed using proper statistical method. **Results:** Left ventricular mass index (LVMI) is significantly higher in diabetic patients as compared to control population ($P<0.001$). It was also observed that the means of the left ventricular posterior wall thickness, interventricular septal thickness, and the left ventricular internal diameter during diastole (in all cases $P<0.001$) were statistically significantly high in diabetic patients in comparison to healthy control subjects. We have found that a significant systolic dysfunction in diabetic group and diastolic dysfunction also very common in diabetic group than the control group. The LVMI also increased in patients who have longer duration of diabetes and poor glycemic control. **Conclusion:** LVM is significantly higher in patients of type 2 diabetic without having hypertension, albuminuria, and apparent ischemic heart disease as compared to healthy controls. LVM in diabetic patients increases with duration of diabetes and is positively correlated with HbA1c and blood sugar level.

Key words: Diabetes mellitus; Left ventricular dysfunction; Left ventricular hypertrophy; Left ventricular mass index; Normotensive

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INTRODUCTION

Cardiovascular disease is increased in individuals living with diabetes mellitus (DM) both type-1 and type-2. The Framingham Heart Study revealed a marked increase in peripheral arterial disease, congestive heart failure (CHF), coronary artery disease (CAD), myocardial infarction, and sudden death (risk increase from one- to five-fold) in DM.[1] Cardiovascular complications account for the highest morbidity and mortality in patients with diabetes, mainly due to CAD and CHF. Diabetes is associated with a high prevalence of hypertension, dyslipidemia, obesity, and microalbuminuria. All are known independent cardiovascular risk factors. Even in populations with low cardiovascular risk, diabetes is associated with an increased incidence of cardiovascular death.[2]

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Degree of increased myocardial muscle mass is a strong and independent risk factor for cardiac morbidity and mortality.[3,4] In addition, the risk of ventricular arrhythmia is increased at least 2 times in the presence of the left ventricular hypertrophy (LVH).[5] The significance of LVH is not widely appreciated in medicine. The Framingham Study showed that increased the left ventricular (LV) mass is associated with a significant excess of cardiovascular mortality and morbidity.[1] This is independent of the presence of CAD or hypertension, with a tripling of the mortality rate in subjects with and without either of these.[1]

LVH, which is an ominous prognostic sign and an independent risk factor for cardiac events, is often present in type 2 DM patients.[6] The possible contributions of hyperinsulinemia and hyperglycemia to the left ventricular mass (LVM) have been suggested in the normotensive and hypertensive subjects without diabetes.[6] Hyperinsulinemia, which is possibly associated with insulin resistance, may promote concentric changes in LV geometry in normotensive and mildly to moderately hypertensive subjects without DM.[7] Hyperglycemia also may be an independent risk factor for concentric changes in LV geometry when subjects with mild DM are included.[7] The pathophysiology of LVH in type 2 DM (T2DM) remains unclear and is not fully explained by the hyperglycemia-associated cellular alterations.[8] There is a growing body of evidence that supports the role of inflammation, oxidative stress, AMP-activated kinase, and insulin resistance in mediating the development of LVH.[8] Diabetic cardiomyopathy, a diabetes-related myopathic state, is characterized mainly by impaired diastolic function.[9] Hence, diastolic dysfunction (D/D) is very common among diabetic subject, though systolic dysfunction is not universally present.

Echocardiography is a reliable non-invasive tool to estimation of LVM and has been proven to be a more sensitive tool for the estimation of LV mass and function than other techniques. Very few studies available from India that examine the risk factors related to LVM and LV function in T2DM patients without hypertension. Hence, the aim of this cross-sectional study is to evaluate the LVH and LV function in normotensive diabetes patients without antihypertensive medication.

Aims and objectives

The study has the following specific objectives:

1. To compare LVM and LVM index (LVMI) between normotensive diabetic and age- and sex matched normotensive, non-diabetic populations.
2. To determine the LV systolic and diastolic function and compare it with age and sex matched non diabetic patient.
3. To find out the prevalence of high LVM in normotensive type 2 diabetic patients and control patients.
4. To uncover the risk factors for the development of high LVM in normotensive type 2 diabetic patients.

MATERIALS AND METHODS

This hospital-based observational study with a cross-sectional design was conducted at SSKM hospital from May 2018 to April 2019. We included all the normotensive patients attending diabetes outpatient department (OPD) and medicine OPD.

Sampling

100 normotensive patients, suffering from T2DM, were randomly selected from diabetes OPD of SSKM hospital and 100 age- and sex-matched normotensive controls were selected from medicine OPD.

Inclusion criteria

The following criteria were included in the study:

a. Diagnosed diabetic patients either on therapeutic lifestyle control or anti-diabetic drugs.
b. Patients who were normotensive and not taking any antihypertensive medication.
c. Age group: 12–65 years.

Exclusion criteria

The following criteria were excluded from the study:

a. Hypertensive patients or patients on anti-hypertensive medication(s).
b. Known causes of LV hypertrophy such as hypertension, cardiomyopathy, aortic stenosis diabetic nephropathy/CKD, and athletes heart.
c. Does not give consent for study.

Tools and techniques

Sphygmomanometer was used to measure blood pressure. Echocardiography was done to measure LVM and systolic and diastolic function of the left ventricle.

Echocardiography

Echocardiography was done using single machine model VIVID 7 (GE company made).We have used single observer to rule out bias.

Calculation of LVEF was done using Teicholz method. We have used M mode in parasternal long axis and measured wall thickness during systole and diastole; we have measured LV cavity dimensions during systole and diastole. Subsequently, in built software calculated the EF. We use the American Society of Echocardiography and the European Association of Echocardiography published guideline for the assessment of diastolic function by echocardiography.[10]

Measurement of LVM: Devereux and Reichek[11] cube formula used to assess LV mass.The formula is LVM=0.8×1.04 ([LVIDD+IVSd+LVPWd]^3–LVIDD^3)+0.6. Echocardiographic assessment of LVMI was done using formula LVMI=LVM/BSA

(LVIDD: Left ventricular internal diameter during diastole, IVSD: Inter-ventricular septal thickness during diastole, LVPWD: Left ventricular posterior wall thickness during diastole, BSA: Body surface area).

Statistical analysis

Collected data were entered in Statistical Packages for the Social Sciences version 20 and checked for completeness. Descriptive and inferential statistics were used to analyze and present it. Normally distributed data from continuous variables were presented in the form mean (±SD) and the data from discrete variables were presented in the form of frequency and proportion. Independent sample t test was performed for normally distributed data from continuous variables and Chi-square test was done for normally distributed data from discrete variables. Correlation was assessed and Pearson correlation coefficient was calculated between LVMI and fasting blood sugar (FBS), post-prandial blood sugar, HbA1C. P<0.05 was considered significant.

Ethical issues

Ethical clearance was taken from Institutional Ethics Committee (Memo No-Inst/IEC/692) before conducting the study.

Informed consent was taken from all the study participants before recruiting them for the study.

RESULTS

Mean age of the diabetic patients was 49.27 (±10.23) years while that of non-diabetic population was 47.17 (±9.44) years and the difference was not statistically significant. The proportion of male (56%) and female (44%) in diabetic patient was not statistically different from that of non-diabetic male (50%) and female (50%) (Table 1). This matching was done to rule out any effect of age and sex on LVM. The mean body surface area of diabetic patients was 1.62 (±0.10) m^2 whereas that of non-diabetic patients was noted to be 1.59 (±0.08) m^2 and the difference was not statistically significant. Diabetic patients' mean fasting and post-prandial glucose level and HbA1C were 144.65 (33.04) mg/dl, 224.87 (54.53), and 7.69 (0.59%), respectively, while the corresponding parameters noted among non-diabetic study participants were 82.44 (10.46) mg/dl, 115.05 (15.18) mg/dl, and 5.73 (0.46)% (Table 1).

Echocardiographic measurements of the left ventricular structure and function revealed that – left ventricular internal dimension in diastole (LVIDD), left ventricular posterior wall thickness (LVPWT), and inter ventricular septal thickness (IVST) – were higher in T2DM patients and left ventricular ejection fraction is lower than non-diabetic subjects and the difference was statistically significant. LVM and LVMI were statistically significantly higher in diabetic patient than non-diabetes normotensive patients (Table 2).

LVMI is considered to be increased when it is more than 115 g/m^2 in males and more than 95 g/m^2 in case of females.[12,13] Increased LVMI was noted among 61% of the T2DM patients while 5% of the non-diabetic subjects had increased LVMI and the difference was statistically significant (Table 3).

Table 1: Socio demographic, anthropometric, and glycemic profile of the diabetic and non-diabetic study participants

Patients profile	Diabetic (100)	Non diabetic (100)	Pvalue
Age in years (±SD)	49.27 (10.23)	47.17 (9.44)	0.130
Sex			
Male (%)	56 (56)	50 (50)	0.395
Female (%)	44 (44)	50 (50)	
BSA in m^2 (±SD)	1.62 (0.10)	1.59 (0.08)	0.09
FBS in mg/dl	144.65 (33.04)	82.44 (10.46)	0.001
PPBS in mg/dl	224.87 (54.53)	115.05 (15.18)	0.001
HbA1C	7.69 (0.59)	5.73 (0.46)	0.001

BSA: Body surface area, FBS: Fasting blood sugar, PPBS: Post-prandial blood sugar

Table 2: Echocardiographic profile of the diabetic and non-diabetic study subjects

Echo parameter	Diabetic Mean (±SD)	Non-diabetic Mean (±SD)	P value
IVSD	10.69 (1.22)	8.85 (0.81)	0.001
LVPWT	10.49 (1.24)	8.82 (0.84)	0.001
LVIDD	46.34 (5.10)	43.84 (3.91)	0.001
LVIDS	30.88 (4.38)	28.24 (3.04)	0.004
LVEF	61.23 (6.53)	65.47 (4.20)	0.001
LVM	186.25 (37.76)	128.38 (25.37)	0.001
LVMI	114.38 (20.33)	80.60 (13.71)	0.001

LVM: Left ventricular mass, LVMI: Left ventricular mass index, LVIDD: Left ventricular internal dimension in diastole, IVSD: Interventricular septal diameter, LVPWT: Left ventricular posterior wall thickness, LVEF: Left ventricular ejection fraction

Table 3: Prevalence of increased LVMI in T2DM and non-diabetic study subjects

LVMI status	T2DM No. (%)	Non diabetic No. (%)	P value
Normal	39 (39)	95 (95)	<0.001
Increased	61 (61)	5 (5)	
Total	100 (100)	100 (100)	

LVMI: Left ventricular mass index, T2DM: Type 2 diabetic mellitus

In this study we found, mean systolic function in diabetes group was 61.23 and that of control group was 65.47. Although statistically significant different exist between two groups (P=0.001), in clinical practice there is no difference in systolic function between groups (Figure 1). If we see the D/D among control and diabetes group we have found, 49% of control group patients had no D/D and 51% patients had only Grade-I D/D but in diabetic group, 53% patients had Grade-I D/D, 37 % patients had Grade-II D/D, and 6% patients had Grade-III D/D. Hence, D/D was increasing in patients with diabetic (Table 4).

Correlation of LVMI was assessed with FBS, post-prandial blood sugar (PPBS) and HbA1C and duration of diabetes. The study revealed positive correlation between LVMI and FBS, PPBS, HbA1C, and duration of diabetes. The Pearson's correlation coefficient was 0.72, 0.66, 0.76, and 0.79, respectively, and the association was statistically significant. The corresponding R2 for FBS, PPBS, and HbA1C and the duration of diabetes were 0.52, 0.44, 0.58, and 0.62 or in other words the study has revealed that 52%, 44%, and 58% variability in LVMI can be explained by FBS, PPBS, and HbA1C, respectively (Table 5 and Figures 2-4).

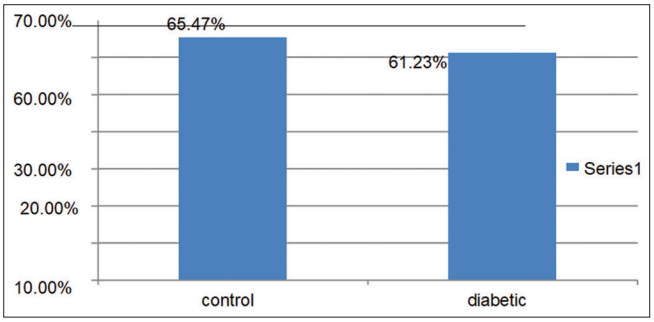

Figure 1: Bar diagram showing the left ventricular systolic function in control and diabetic patients

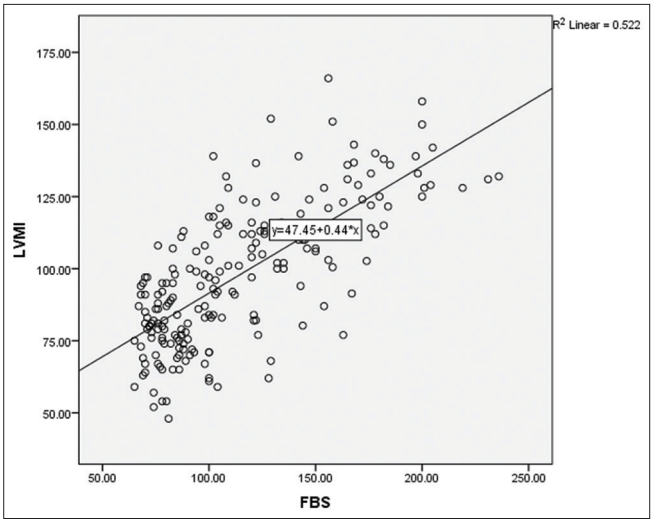

Figure 2: Correlation of LVMI with FBS. LVMI: Left ventricular mass index, FBS: Fasting blood sugar

DISCUSSION

Majority of patients with DM eventually suffer from cardiac ailment and DM remains crucial factor in overall diabetic morbidity and mortality. Increased LVM may contribute to the increased cardiovascular risk because LVH is an important prognostic sign and an independent risk factor for sudden death, ventricular dysrhythmia, myocardial ischemia, coronary heart disease, and heart failure.

Our cross-sectional study demonstrated that increased LVMI is to be a common association in normotensive type 2 diabetic patients predominantly without micro- or macr-ovascular complications and hypertension compared to the age- and sex-matched, normotensive, and non-diabetic control population. In our study group, none of the patients were receiving antihypertensive medication. In this study, LVM and LVMI were compared with the BSA to avoid the influence of obesity. We also observed that the mean of LVM and LVMI was statistically significantly high (in both case P<0.001) in diabetic patients in comparison to healthy control subjects. This indicates the association of high LVM in patients of DM. A study from Japan demonstrated that LVM and LVMI were significantly greater in the normotensive T2DM patients than the normotensive control population, by

Table 4: Diastolic dysfunction in control and diabetic group (N=100)

Diastolic dysfunction grading	Groups		Total
	Control	Diabetic	
D/D			
0			
Count	50 (92.6%)	4 (07.4%)	54 (100%)
% within Groups	50	4	24.8
I			
Count	50 (48.5%)	53 (51.5%)	103 (100%)
% within Groups	50.0	53.0	52.0
II			
Count	0	37 (100%)	37 (100%)
% within Groups	0.0	37.0	18.3
III			
Count	0	6 (100%)	6 (100%)
% within Groups	0.0	6.0	3.0

Table 5: Correlation of LVMI with glycemic status of the study variables

Glycemic status	Pearson's correlation co-efficient	R^2	P value
FBS	0.72	0.52	<0.001
PPBS	0.66	0.44	<0.001
HbA1C	0.76	0.58	<0.001
Duration of diabetes	0.79	0.62	<0.001

LVMI: Left ventricular mass index, FBS: Fasting blood sugar, PPBS: Post-prandial blood sugar

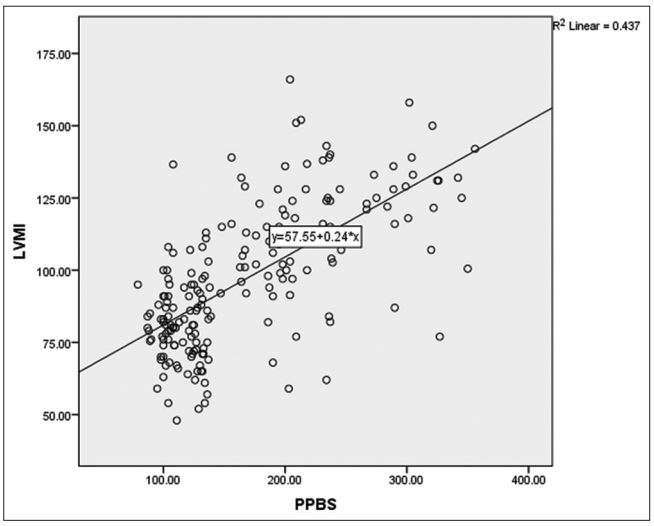

Figure 3: Correlation of LVMI with PPBS. LVMI: Left ventricular mass index, PPBS: Post-prandial blood sugar

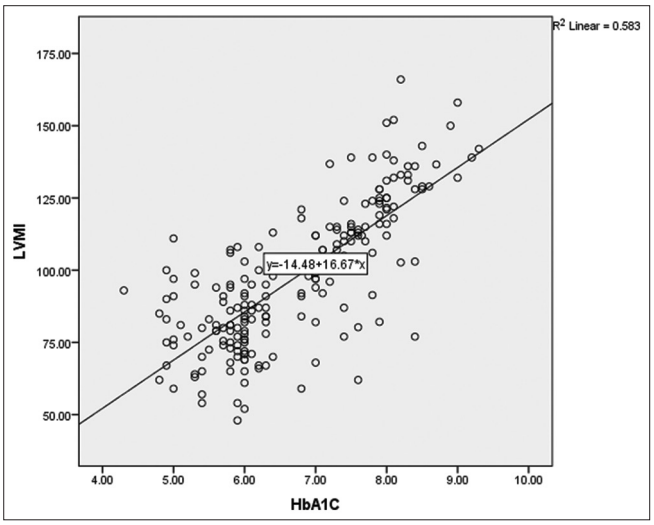

Figure 4: Correlation of LVMI with HbA1C. LVMI: Left ventricular mass index

Hirayama et al.,[3] Hence our results corroborated with that study.

In our study, it was also observed that the mean values of LVPWT, IVST, and LVIDD (in all cases P<0.001) were statistically significantly high in diabetic patients in comparison to healthy control subject. The increased ventricular wall thickness and left ventricular dilatation, both contribute to the observed increase in LVM. This study shows that cardiac muscle disease complicates diabetes in subjects who do not have hypertension. In this study, we also found that there is a significant difference in LVM between normotensive, T2 DM patients and the control group. Diabetic patients had higher relative wall thickness (0.50 vs. 0.44, P<0.001) and higher prevalence of concentric LV hypertrophy (39.4% vs. 26.8%, P<0.001) than non-diabetic patients.[14] This finding is important as increased LVM is contributor to increased cardiovascular morbidity and mortality. Hence, early diagnosis and prevention is important to prevent patients from sufferings; drug therapy can lead to improvement in the left ventricular function and can decrease cardiovascular morbidity. The high prevalence of LVH in diabetic patients supports this idea that early echocardiographic screening is prudent and may be beneficial to these patients.

The prevalence of LVH in the predominantly non-diabetic population (CI 95%) calculated in the Framingham Heart Study assessed by echocardiography was reported to be 16% in men and 21% in women. In our study, the prevalence of increased LVMI (normal upper limit for LVMI in female <95 g/m^2 and in male <115 g/m^2)[12,13] was 4.9% (2% in male and 7.8% in female) in control population but 60% (46% in male and 79.5% in female) is significantly higher. The prevalence of LVH increases with the severity of hypertension, ranging from 38% to 72% in hypertensive diabetic populations.[14] In the present study, nearly 60% of patients had LVH, even though none of the included type 2 diabetic patients was receiving or had prior treatment with antihypertensive medications, and all had an arterial blood pressure below the recommended cutoff of 140/90 mmHg. While other studies have found a relationship between arterial blood pressure and LVM in diabetic patients with and without hypertension, this was not the case in the present study, where blood pressure levels were lower. Interestingly, in non-diabetic population, LVH is commonly associated with ischemic heart diseases and vice versa; however, evidence suggests that ischemic heart disease is a consequence rather than cause of LVH. A cohort of more than 5000 patients and found that the increased wall thickness of the ventricular septum or of the left ventricular posterior wall was not associated with prevalent coronary heart disease by Lee et al.,[4] Consequently, our findings of an increased wall thickness could not be explained by such a mechanism. Although this study was conducted with normotensive patients, it appeared clearly that features of diabetic cardiomyopathy were associated with increasing blood pressure levels. Increasing blood pressure could either be an etiologic factor or simply part of the hemodynamic features of diabetic cardiomyopathy as reported in experimental studies.

An increased heart size may reflect the increase in the circulating blood volume and systolic dysfunction could be secondary to increased peripheral resistance, as some studies have shown increasing peripheral resistance in diabetic patients. We have found a statistically significant difference of systolic function in diabetic patients in comparison to non-diabetic non hypertensive patients. This could therefore be attributable to early changes

preceding established hypertension. Our study also showed that D/D was increasing in patients with diabetic without hypertension than the control group. This D/D is explained by the increase LVM as found in diabetic group of patients. In humans, left ventricular D/D (LVDD) is considered the earliest manifestation of diabetic cardiomyopathy, preceding the development of systolic dysfunction.[16] Patients with T2DM had an additional worsening in diastolic function parameters, such as E' velocity and E/E' ratio, and a further increased prevalence of LVDD.[17] A positive correlation between severity of CAD assessed using SS and E/A and E/e' and LAVI which are various determinants of DD, was found from a study conducted by Mukhopadhyay et al.,[18] Diastolic function seems more susceptible to ischemia than systolic function and can take longer to recover.[19,20] So this increase association of D/D in patients with diabetes as shown in our study, is also an important predictor of adverse cardiovascular outcome, early detection and treatment may improve morbidity and mortality in the diabetic patients.

In our study, type 2 diabetes patients with common risk factors for the development of LVH, such as hypertension, albuminuria, thyroid disorder, ischemic heart diseases, and dyslipidemia were excluded from the study. We have found that the LVMI increased with the longer duration of diabetes and poor glycemic control as suggested by higher HbAIc in the diabetic population with LVH. Sato et al., also reported a significant correlation between glycemic control, duration of DM, and severity of nephropathy and LVMI.[21] That urinary albumin excretion rate is strongly associated with the degree of LVM hypertrophy has been demonstrated in several previous studies of non-diabetics and type 1 and type 2 diabetic patients with micro and macroalbuminuria.[22] Furthermore, in hypertensive diabetic and non-diabetic patients with LVH, an increased urinary albumin excretion rate resulted in an increased risk for cardiovascular morbidity and mortality.[23] However, in our study, we had selected the patients from both diabetic and healthy control groups, those having no micro- and macroalbuminuria. Hence, in this study, albuminuria was not the cause of LVH. In addition to blood pressure, urinary albumin excretion rate, BMI, and blood glucose,[24] it has also been suggested that coronary microvascular dysfunction, endothelial dysfunction and chronic inflammation, and abnormalities in the tissue renin–angiotensin–aldosterone–bradykinin system or the encoding genes might play a role in the pathogenesis of LVH.[25] The observation that some type 2 diabetic patients have asymmetrical and some have concentric hypertrophy might suggest that the underlying pathology is not homogenous, but rather reflects the interaction of several of the above-mentioned risk factors.

Limitations of the study

Few limitations of our study are: (1) No molecular analysis was done why LVH occurs in diabetes. (2) We must say that this type of study demands much more time and more number of patients. (3) No long term follow-up was done. (4) No coronary angiogram was done. Ischemic heart disease was ruled out only by ECG and echocardiogram. However, further studies with a larger cohort of patients are needed.

CONCLUSION

Our case–control study showed that LVM is significantly higher in type 2 diabetic patients without hypertension as compared to healthy compatible control group. The diastolic and systolic dysfunction also increases in patients with diabetes without hypertension. Hence, LVM screening is a mandatory workup in all T2DM patients for the prognostication of morbidity and mortality. LVM is increased with the duration of diabetes. LVM is also increased with the HbAIc level and a poor glycemic control. Hence, patients with a longer duration of diabetes with poor glycemic control have more chances of having LVH. Hence, a large, prospective, double-blind study design will further reveal the actual prevalence of LVM in such population. Our study in that sense is a sort of eye opener work.

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Authors' Contributions:
TM- Concept and design of the study, reviewed the literature and manuscript preparation; **PS**- Concept and design of the study, Interpreted the results; prepared first draft of manuscript, reviewed the literature, and manuscript preparation; **UB**- Coordination, statistical analysis and interpretation, preparation of manuscript, and revision of the manuscript; **SN**- statistical analysis and interpretation and revision of the manuscript; **SISK**- Concept and design of the study, interpretation, and revision of the manuscript.

Work attributed to:
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Clinical profile of seizure disorder in hospitalized patients in tertiary care center - A prospective cross-sectional study

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ABSTRACT

Background: Knowledge regarding people affected with epilepsy is essential for accurate planning and management of patients. This study was conducted to study clinical profile of seizure disorder in the patients hospitalized in a tertiary care hospital of Tamil Nadu. **Aims and Objectives:** To study clinical profile of seizure disorder in patients hospitalized in Coimbatore government medical college hospital. **Materials and Methods:** This study was a single center hospital based cross-sectional study of the clinical profile of seizure disorder in hospitalized patients at tertiary care center of Tamil Nadu, Neurology department the 2 years from 2018 to 2020. All the patients presenting with complaints of seizures were included in this study. **Results:** This study included a total of 321 patients with epilepsy. Their ages ranged between 10 and 100 years. 180 of the study population were males and 141 were female patients. 30% of patients had new onset seizures. Fever precipitated seizure in 16% of the subjects. Excitation, sleep deprivation, fever, watching television, and head trauma showed a strong association with generalized epilepsy. The majority of the patients had generalized tonic-clonic seizure, followed by focal neurological deficit. 98% of patients responded to treatment and they did not had recurrent episodes of seizure. **Conclusion:** The sample size of our cohorts is relatively small. It is possible that some prognosis factors may be missed due to the small sample size. Further studies with a larger sample cohort are required. Uneducated and low socioeconomic make people vulnerable to seizures because of lack of awareness, poor compliance to medicines, not detection of seizure provoking factor, repeated exposure to seizure provoking factor, prevalence of alcoholism, and thus lowering seizure threshold. There is a treatment gap still because of epilepsy and appropriate usage of resources will help to reduce this treatment gap and decreases epilepsy associated morbidity and mortality.

Key words: Epilepsy; Focal; Generalized seizures; Generalized; Seizures

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INTRODUCTION

Epilepsy is a common medical and social disorder or group of disorders with unique characteristics. Epilepsy was defined conceptually in 2005 as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having two unprovoked seizures >24 h apart. The International League Against Epilepsy accepted recommendations of a task force altering the practical definition for special circumstances that do not meet the two unprovoked seizures criteria. The task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. The word "epilepsy" is derived from Latin and Greek words

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for "seizure" or "to seize on."[1] The periodic clinical features of seizures are often dramatic and alarming, and frequently elicit fear and misunderstanding. This, in turn, has led to profound social consequences for sufferers, which has greatly added to the burden of this disease. In ancient times, epileptic attacks were thought to be the result of invasion and possession of the body by supernatural forces, usually malign or evil influences, requiring exorcism, incantations or other religious or social approaches.[2] Despite scientific advances in the 19th century, epilepsy remained a profound social problem compounded by deeply rooted historical concepts of a supernatural or sacred disorder.[3] Widespread ignorance, fear, misunderstanding and stigma contributed to severe legal and social penalties. Epilepsy affects people of all ages, both sexes, and all ethnic groups. Children under the age of 2 and adults over 65 are more likely to develop epilepsy than any other age group. This is explained in part by changes that occur in the brains of people early and late in life. During childhood brain development, for example, seizures are not only more likely to occur, they also spread more readily than in a fully developed brain.[4] The rise in the incidence of epilepsy in adults as they age is due to changes in the brain caused by tumors and strokes and other brain abnormalities.

Aims and objectives

To study clinical profile of seizure disorder in patients hospitalized in Coimbatore government medical college hospital.

MATERIALS AND METHODS

This study is a single center hospital based cross-sectional study of clinical profile of seizure disorder in patients hospitalized in Coimbatore government medical college. The study was conducted after receiving approval from the Institutional Human Ethics Committee. All patients presented with seizures were included in our study. Those unwilling to participate and those unavailable during the study period were excluded from the study. The study was conducted over a period of 2 year.

Statistical analysis

Statistical analysis was carried out for 321 patients with complaints of seizures. Statistical analysis was done using SPSS version 21, and the results are expressed in percentages.

RESULTS

A total of 321 patients were included in the study out of which 24 patients were from 10 to 20 years of age group, 21 patients were from 20 to 30 years of age group, 33 patients were from 30 to 40 years of age group, 42 patients were from 40 to 50 years of age group, 63 patients were from 50 to 60 years of age group, 54 patients were from 60 to 70 years of age group, 42 patients were from 70 to 80 years of age group, 30 patients were from 80 to 90 years of age group, 12 patients were from 90 to 100 years of age group. Maximum number of the patients were in 50–60 years and least number of the patients were in 90–100 years. The prevalence of active epilepsy is 6.4/1,000 and the lifetime prevalence is 7.6/1,000. The prevalence tends to increase with age, with peaks in the oldest age groups and in socially deprived individuals. The incidence of epilepsy is 61.4/1,00,000 person-years. Epilepsy has a bimodal distribution according to age with peaks in the youngest individuals and in the elderly.[5] The increased incidence of seizures and epilepsy in the elderly can be attributed to the increase of age-related and aging-related epileptogenic conditions (Table 1).

A total of 321 patients of which 180 were males and 141 females. Even though there is no overall gender difference in seizure disorder. In our study, seizure disorder was more in males. Overall, no gender difference was found in localization-related epilepsy, but localization-related symptomatic epilepsies were more frequent in men, and cryptogenic localization-related epilepsies were more frequent in women (Figure 1).

Table 1: Age distribution

Age	Number of patients
10–20	24
20–30	21
30–40	33
40–50	42
50–60	63
60–70	54
70–80	42
80–90	30
90–100	12

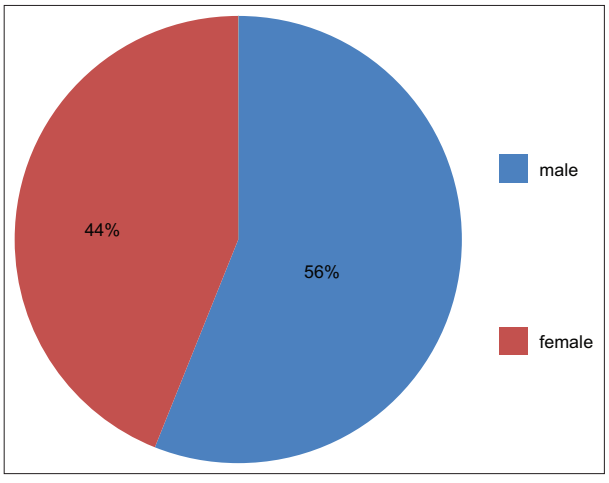

Figure 1: Sex distribution

The relationship between alcohol and seizures is complex and multifaceted. The seizure threshold is raised by alcohol drinking and declines on cessation of drinking. As a result, during withdrawal from alcohol, usually 6–48 h after the cessation of drinking, seizures may occur. Alcohol acts on the brain through several mechanisms that influence seizure threshold. These include effects on calcium and chloride flux through the ion-gated glutamate NMDA and GABA receptors. During prolonged intoxication, the CNS adapts to the effects of alcohol, resulting in tolerance; however, these adaptive effects seem to be transient, disappearing after alcohol intake is stopped. Although the relationship of seizures to alcohol use is likely to be dose dependent and causal, the available clinical data do not suggest that alcohol use results in seizure genesis.[6] However, a genetic predisposition to alcohol withdrawal seizures is possible.

The ingredients and chemicals in cigarettes could increase problems with the central nervous system. Be proconvulsant and other times anticonvulsant. Pose serious risks for people who already are epileptic. Cause seizures in those who have never suffered an epileptic episode before. In our study, the following chart indicates percentage of smokers, alcoholic, and non alcoholic (Figure 2).

Last seizure episode

About 30% of patients had new onset seizures. 20 % patients had seizure 6 months back. 15% had last seizure episode 1 year back. Few did not remember there last seizure episode. 4% patients had seizure episode within 1 week.

Seizure provocative factor

In most of the cases seizure occurs spontaneously, but there may be association with various triggers. These triggers may act as seizure precipitating factors (SPFs). All participants were interviewed through a predesigned close ended questionnaire that included a long list of 20 precipitating factors. Fever precipitated seizure in 16% of the subjects. A good number of them 17% noticed that whenever there was sleep deprivation, they had an attack of epilepsy. However, drug withdrawal, playing outside and head trauma were also common among the patients, about 15%, 8% and 12%, respectively. The most of the patients can identify their seizure precipitant and clustering of many SPFs suggests a common pathophysiologic mechanism for these triggers.[7] Excitation, sleep deprivation, fever, watching television, and head trauma showed a strong association with generalized epilepsy. Patients with seizure disorder should be evaluated for presence of SPFs, because identification of these might help in proper management of epilepsy. Patients' knowledge of seizure precipitants was poor. The majority of hospital admissions for seizures in epileptic patients are associated with potentially preventable causes amenable to education programs. Patient education involving epilepsy nurse educators may play an important role in decreasing seizure occurrence and possibly unnecessary hospital admissions (Figure 3).

Demography

In our study population, 75% of patients fall under low socioeconomic group and 73% of people are uneducated. Hence, uneducation and low socioeconomy make people vulnerable to seizures because of lack of awareness, poor compliance to medicines, not detection of seizure provoking factor, repeated exposure to seizure provoking factor, prevalence of alcoholism and thus lowering seizure threshold etc.

Types of seizures

Seizures were broadly classified in to 3 types Focal seizures, generalized seizures and lastly unclear epileptic spasm. Focal seizures can be classified in to focal seizures with intact awareness and impaired awareness. Generalized seizures were again classified into 5 types they are (1) absence seizures, (2) Tonic-clonic seizure, (3) clonic, (4) Atonic, and (5) Myoclonic seizure. Among total of 321 patients in our study 45 patients had focal seizures,

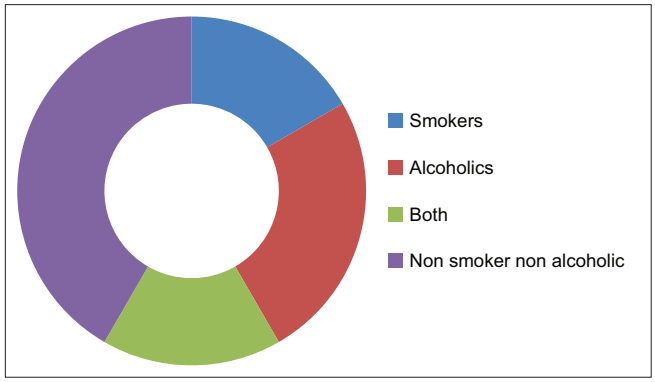

Figure 2: Smoking and alcohol distribution

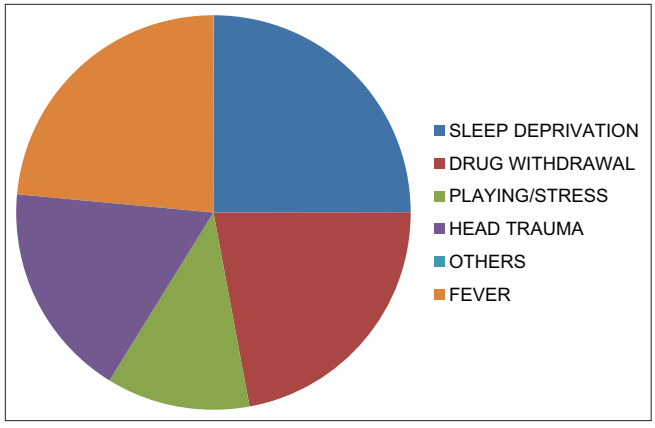

Figure 3: Seizure provocative factor

210 patients had generalized seizures and others were unclear epileptic spasm.

Provoked versus unprovoked seizure

A provoked seizure has a direct cause such as a head injury, an infection or low blood sugar. An unprovoked seizure does not have an immediate cause. In our study, about 80 patients had provoked seizures out of 321 patients. Moreover, 241 patients had unprovoked seizure. Provoked seizures contribute to 25% of seizures.

Past medical illness

Many medical illnesses can cause seizures. Metabolic derangements, such as disorders of serum glucose metabolism, cause seizures, as well as other neurologic manifestations. In our study, out of 321 patients 159 patients were diabetics among diabetics 93 were male and 66 were female; there were 141 hypertensive patients out of which 81 were females and 60 were males. There wasabou72 CKD patients out of which 21 patients were on hemodialysis. 12 diabetic patients came with hyperglycemia and focal seizures. 36 patients had history of RTA. 45 patients had CVD. 6 patients had developmental delay.

Clinical profile

Almost all patients with generalized seizures had postictal confusion. Maximum duration of postictal state was about 24 h and minimum duration of postictal state was about 30 min. 45 patients had slurring of speech. 78 patients had neck stiffness. 45 patients had fecal incontinence. 135 patients had focal neurological deficit. 54 patients have bitten there tongue.

Drug withdrawal seizures

Patients who are on antiepileptics are at high chance of getting seizure if they suddenly stop antiepileptic drug. In our study, 18 patients who were on anti-epileptic drugs (AEDs) presented with seizures due to stoppage of medication.

Response to treatment

About 98% of patients responded to treatment and they did not had recurrent episodes of seizure. 2% had refractory seizures. All patients were monitored for 48 h for any recurrent episodes of seizures. The sample size of our cohorts is relatively small. It is possible that some prognosis factors may be missed due to the small sample size. Further, studies with a larger sample cohort are required.

Brain imaging

Due to lack of resources imaging was not done in all patients. Among our study patients, 198 patients underwent CT and 60 patients underwent MRI imaging. 135 patients had normal study. 60 patients had acute or chronic infarct. Brain edema was found in 57 patients. Ideally, MRI brain with epilepsy protocol should have been investigation of choice but because of practical constraints MRI was not done in all patients.

EEG

Sixty six patients had abnormal epileptiform activity in EEG. 105 patients had normal EEG study. A few patients missed EEG.

Maximum number of the patients presenting with seizure were being diagnosed as stroke and tumors being least cause for seizure (Table 2).

DISCUSSION

Neurological diseases are the most common disease among all the diseases in the word and among that seizure disorder

Table 2: Age distribution of adult onset seizures

Diagnosis	Age distribution (years)						Total
	Under 20	21–30	31–40	41–50	51–60	Above 60	
Stroke	2	5	6	12	25	36	86
Percentage							26
CNS infection	8	5	5	6	14	18	56
Percentage							17
Metabolic	9	4	7	8	7	26	61
Percentage							19
Brain tumors	1		2		3	7	13
Percentage							4
CVT		4	6	4	4	8	26
Percentage							8
ADEM			2	4	4	12	22
Percentage							6
PRES			1	2	2	6	11
Percentage							3
Idiopathic	4	3	4	6	4	25	46
Percentage							14
Total	24	21	33	42	63	138	321

is one of the most common disease causing morbidity and premature mortality. The spectrum of seizure disorder varies based on demographic profile of the patients. Hence, the knowledge of profile of patients in different clinicosocial environment is a necessity. Infections (neurocysticercosis, tuberculoma, meningitis, and malaria) were the hidden spurious causes followed by idiopathic. In the study by Quraishi et al.,[8] tuberculoma accounts for 14% and in Thapa et al.,[9] study, it accounts for 10%. The incidence was high in studies of Ramamurthi et al., (19.4%)[10] In this study, alcohol related seizures formed 15% of cases. the findings of Rathlev et al.,[11] where 53.6% patients had causes other than alcohol withdrawal. Maximum number of the patients presenting with seizure were being diagnosed as stroke 25% either acute or chronic and tumors being least cause for seizure. In >65 years age, vascular causes were the most common. In 18–25 years age group, Infections (neurocysticercosis, tuberculoma, meningitis, and malaria) were the most common cause followed by idiopathic. In middle 26–45 years age group, infections such as neurocysticercosis, tuberculoma, meningitis, malaria, and toxoplasma were the most common cause followed by idiopathic followed by vascular which included arterial and venous infarcts and intracranial bleed. GTCS was the most common type of seizure cases.

Limitations of the study

Some prognosis factors may be missed due to the small sample size.

CONCLUSION

Epilepsy is a common neurological problem. It can profoundly affect life of people. The sample size of our cohorts is relatively small. It is possible that some prognosis factors may be missed due to the small sample size. Further, studies with a larger sample cohort are required. Uneducation and low socioeconomy make people vulnerable to seizures because of lack of awareness, poor compliance to medicines, not detection of seizure provoking factor, repeated exposure to seizure provoking factor, prevalence of alcoholism, and thus lowering seizure threshold. There is a treatment gap still because of epilepsy and appropriate usage of resources will help to reduce this treatment gap and decreases epilepsy associated morbidity and mortality.

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Assessment of cardiovascular sympathetic function tests in premenstrual syndrome patients visiting tertiary care hospital: A case–control study

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ABSTRACT

Background: Premenstrual syndrome (PMS) is a stress-induced disorder and is showing a rising prevalence but its etiopathogenesis is not yet understood. Stress disturbs the balance of the sympathetic and parasympathetic nervous system. Alteration in heart rate and blood pressure is the most important physiological response following stress-induced sympathetic changes. **Aims and Objectives:** The present study was designed to test the hypothesis of an association between sympathetic functions and PMS and to observe the degree of changes (if any) in these sympathetic functions. The study also aims to provide timely interventions to prevent the development of cardiovascular complications and improve lifestyle. **Materials and Methods:** A Menstrual Distress Questionnaire was used to evaluate physical, emotional, and behavioral symptoms accompanying the menstrual cycle of the subjects who fulfilled the inclusion criteria. Based on the scores obtained by their questionnaire, subjects with the higher scores formed the PMS group, while the age-matched females with low score served as controls. Cardiovascular sympathetic functions were assessed by standardized, simple, non-invasive tests which included Handgrip test and orthostatic hypotension test. Unpaired Student's t-test was used for statistical analysis. **Results:** The results revealed that the sympathetic reactivity is insignificantly higher in PMS group during the follicular phase. During the luteal phase, sympathetic activity is significantly increased. **Conclusion:** PMS involves psychoneuroendocrinal turmoil, thus early screening of high-risk groups and interventions such as relaxation techniques and lifestyle modification can prevent further cardiovascular complications in patients of high sympathetic responses.

Key words: Hand grip test; Orthostatic hypotension test; Premenstrual syndrome; Sympathetic function tests

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INTRODUCTION

Premenstrual syndrome (PMS) is a major clinical entity affecting a large segment of the female population. PMS is a psychoneuroendocrine disorder describing a range of emotional, behavioral, and physical symptoms that occur during the luteal phase of the menstrual cycle and abate following menstruation.[1] Up to 18% of women have severe PMS that causes significant impairment in term of family/social relationships and quality of life.[2] Some studies show higher heart rate (HR), greater skin conductance, or greater norepinephrine levels throughout the menstrual cycle[3,4] or just in the late-luteal phase in women with severe PMS[5] others show no differences in these measures compared to controls.[6] Many behavioral and neurological symptoms such as headache, malaise, nervous irritability, and emotional instability are reported during the premenstrual phase.[7] PMS is a stress-induced disorder and is showing a rising

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prevalence but its etiopathogenesis is not yet understood. Stress disturbs the balance of the sympathetic and parasympathetic nervous system. Alteration in HR and blood pressure (BP) is the most important physiological response following stress-induced sympathetic changes. To the best of our knowledge, only a few studies have well documented the associations of sympathetic functions with two phases of the menstrual cycle and in relation to the presence of premenstrual symptoms. This stipulated the need of performing sympathetic function tests particularly in the north-western region of Uttar Pradesh. Thus, keeping the aforementioned background in mind, the present study was designed to test the hypothesis of an association between sympathetic functions and PMS, to reconfirm if the activity of the sympathetic nervous system is altered during PMS and also to know its magnitude during the menstrual cycle of women with different grades of premenstrual symptomatology. The study also aims to provide timely interventions to control the further progression of symptoms.

Aims and objectives

To find the association between sympathetic functions and premenstrual syndrome. An association between sympathetic functions and premenstrual syndrome and to observe the degree of changes.

MATERIALS AND METHODS

This case–control study was conducted in the Department of Physiology, LLRM Medical College and associated Hospital, Meerut, between October 2010 and April 2012. The procedures were non-invasive and were approved by the Institutional Ethical Committee of LLRM Medical College. The experiment protocol was explained to the participants and informed written consent was obtained.

Type of study

This is an observational study of case–control design.

Study area and setting

This study was conducted at LLRM Medical College and associated Hospital, Meerut.

Study period

The study was carried out for a period of 8 months. The data collection phase was from January 2011 to December 2011. Data analysis and interpretation were done from January 2012 to February 2012. Final reporting was done from March 2012 to May 2012.

Study population

The study population included all the female patients visiting gynecology OPD.

Study unit

All the female patients in the study population were diagnosed as cases of PMS. These subjects served as a case group. The control group included age-matched healthy participants.

Sample size

The study was conducted on 45 subjects. Out of 21 were cases and 24 were control group.

Sampling technique

The sample was selected from the study population using the judgmental/purposive sampling technique.

Selection criteria

Inclusion criteria

Willing females, age 18–35 years, and regular menstrual cycle were included in the study.

Exclusion criteria

Subjects not giving consent for the study, menstrual disorders, acute, or chronic abdominal pain related to surgical or medical illness, diabetes mellitus, hypertension, cardiovascular disease, syncopal spells, giddiness on standing, steroid therapy, or any other drugs that may alter the sympathetic response, subject receiving psychiatric treatment, smoking, alcohol, or any other recreational drug were excluded from the study. Dropouts were also excluded from the study.

Study tools

A Menstrual Distress Questionnaire was used to evaluate physical, emotional, and behavioral symptoms accompanying the menstrual cycle[8] of the subjects who fulfilled the inclusion criteria. Based on the scores obtained by their questionnaire, the subjects were classified into two groups. Subjects who reported at least one of the affective and somatic symptoms during the 5 days before menses in each of the three prior menstrual cycles served as PMS group, while the age-matched females with low scores in the Menstrual Distress Questionnaire served as controls.[9] The sample size was calculated using a formula for a quantitative observational study.[10]

Details regarding family history of hypertension, coronary artery disease, and sudden cardiac death were obtained. General examination including measurement of weight and height and systemic examination was done. After detailed history and physical examination, the participants were assessed for the menstrual cycle phase by the date of onset of menstruation.

- Premenstrual phase – 5 days before the due date of menses.
- Postmenstrual phase – 5–10 days of the menstrual cycle.

Study techniques

Cardiac autonomic neuropathy is diagnosed by tests of autonomic reactivity based on Ewing's criteria.[11] Cardiovascular sympathetic functions were assessed by standardized, simple, non-invasive tests using sympathetic reflexes. Sympathetic functions of the participants were tested during the follicular and late luteal phases and follow-up assessments were made during both the phases for three consecutive cycles and the average of three values was taken as final reading for that test. Each test was performed under thermoneutral conditions and at the same time of day in all the subjects. The tests were conducted according to the recommended protocol used in clinical studies.[11,12] The subjects abstained from coffee, tea, or cola for 6 h before the study. A light breakfast was allowed 2 h before tests. All the measurements were performed between 11.30 am and 2.30 pm, after recruiting the PMS patients from the gynecology clinic of the associated hospital. The tests were performed in an isolated autonomic function laboratory of the Physiology Department, the temperature of which was maintained between 25°C and 27°C.

The weight of subjects was recorded using the classical weighing machine. Height was measured by stadiometer to nearest 1 cm and weight by weighing machine (Krups) to the nearest 1 kg with subjects standing without shoes and wearing light clothes. After a rest for 15 min basal HR, systolic BP (SBP) and diastolic BP (DBP) was recorded. An electronic automatic ECG recording machine (ASPEN) was used to record lead II ECG and HR. Other apparatus used for tests included timer, automatic BP recording machine (OMARON), and Handgrip dynamometer (25 kg model, IMI, Delhi). Basal BP and HR were measured in the supine position after taking a rest for 5 min.

Tests for a sympathetic component of the autonomic system

BP response to standing (orthostatic hypotension test)

The subject was asked to take a rest for 5 min in the supine position, and then to stand up immediately remaining still, when instructed to do so. BP was recorded immediately and then at 30 s intervals for 2 min or till BP returns to normal. The difference between readings of SBP in the supine position and standing position was calculated. The highest fall in SBP was taken as a response to the test. The fall in SBP more than and equal to 30 mmHg is abnormal.[8]

BP response to sustained hand grip

Basal BP was recorded in a sitting position and then the participant was asked to perform maximum grip of the handgrip dynamometer with her dominant hand and the maximum capacity was noted (Maximum voluntary contraction).

After a rest of 5 min, she was again asked to hold her grip with 30% of her maximum voluntary contraction capacity for 2 min. The BP was recorded simultaneously from the non-exercising arm at the 1st and 2nd min followed by releasing of grip and recording of the BP in the 4th min. The highest difference between the rises in DBP just after the release of the grip to the basal DBP was taken as the test response. An increase in diastolic pressure ≤10 mmHg is abnormal.[11,12]

Test	Normal	Borderline	Abnormal
BP response to standing (fall in systolic BP)	<10 mm Hg	11–29 mm Hg	>30 mm Hg
BP response to sustained handgrip (increase in diastolic BP)	>16 mm Hg	11–15 mm Hg	<10.mm Hg

Ewing's classification of cardiac sympathetic functions into normal, borderline, and abnormal.[12]

Statistical analysis of data

All the results were expressed in mean±S.D. and compared with the control group. The data were analyzed by Statistical Product and Service Solution software for windows and Microsoft Excel. Unpaired Student's t-test was used to find out the level of significance between the two groups. $P<0.05$ was considered statistically significant.

RESULTS

A comparative study of resting HR, SBP, and DBP showed no significant difference between cases and control groups in either phase of the menstrual cycle (Table 1).

Sympathetic responses between control and PMS groups during the follicular phase exhibits an increase in sympathetic activity in the PMS group as compared to control ones though there was no statistically significant difference (as the $P>0.05$) as per (Table 2).

A comparative study of sympathetic functions during the luteal phase reflected mean values of OHT as 6.00±2.09 and 10.58±1.61 in the control group and case group, respectively, which showed statistically insignificant higher sympathetic responses in premenstrual cases ($P = 1.97$). HGT responses in the luteal phase indicate a highly statistically significant ($P = 0.0001$) increase in sympathetic activity in premenstrual cases, with mean values of 12.75±3.32 and 16.85±3.5 in control group and cases (Table 3).

The results revealed that the sympathetic reactivity is insignificantly higher in the PMS group during the follicular

Table 1: Comparative study of resting HR, SBP, and DBP

	Follicular phase		Luteal phase	
	Cases	Control	Cases	Control
SBP (mm Hg)	115.91±7.30	116.5±5.47	117.08±6.77	117.2±5.15
DBP (mm Hg)	74.41±5.98	77.24±6.91	75.25±5.10	77.24±6.37
HR (beats/min)	77.66±5.67	76±6.16	78.08±6.05	75.33±5.37

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate

Table 2: Sympathetic function test in follicular phase

Sympathetic function parameters	Follicular phase		
	Control (n = 21)	Cases (n = 24)	P value
OHT (mm Hg)	5.04±2.15	6.08±2.24	0.12
HGT (mm Hg)	17.33±2.39	17.50±4.38	1.95

Table 3: Sympathetic function test in luteal phase

Sympathetic function parameters	Control (n = 21)	Cases (n = 24)	P value
OHT (mm Hg)	6.00±2.09	10.58±1.61	1.97
HGT (mm Hg)	12.75±3.52	16.85±3.5	0.0001

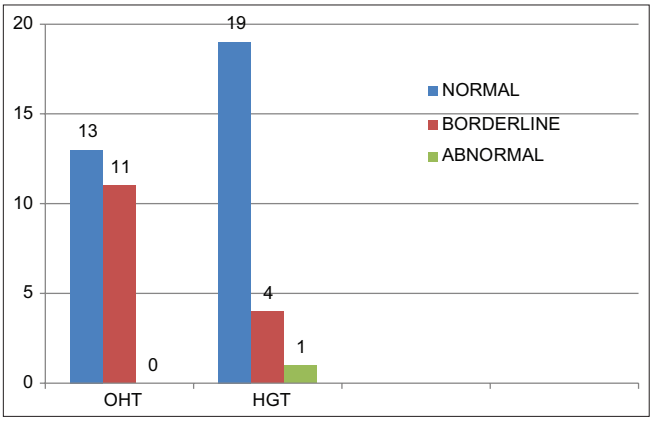

Figure 1: Number of females of premenstrual syndrome showing normal, borderline, and abnormal values in sympathetic autonomic function tests according to Ewing's classification of values of cardiac autonomic function tests

phase. During the luteal phase, sympathetic activity is significantly increased.

Considering the number of females falling in the normal, borderline, and abnormal category of sympathetic function test in PMS case group (Figure 1), abnormal values are obtained in only one case in Handgrip test and 11 cases showed borderline test results. In reference to the orthostatic hypotension test, about four cases got borderline values and none got abnormal values.

DISCUSSION

PMSs are characterized by physical and/or affective symptoms that occur in the luteal phase of the menstrual cycle. PMS affects about 25% of women with a regular menstrual cycle, depending on the strictness of the criteria.[9] Changes in the autonomic function may be responsible for some of the symptoms produced through endorphins and have been held responsible for behavioral changes.[13,14] According to Tamaki, women with a greater degree of premenstrual distress possess higher sympathetic activity in the late luteal phase than women with fewer symptoms.[15] Stimuli that raise BP, such as isometric exercise, or mental arithmetic, activate mainly sympathetic outflow.[16] The present study investigated differences in sympathetic responses between the "baseline" follicular and the premenstrual phases among the premenstrual cases and controls. Table 1 gives the resting HR, SBP, and DBP of cases and control groups in follicular and luteal phases of the cycles, respectively. Some studies[17,18] reported a statistically significant rise in systolic and DBP in females with PMS.[17] However, our study is not in concordance with other researchers as no significant difference was observed in these parameters between cases and control groups in either phase of the menstrual cycle. The difference in results could be due to the large sample size in other studies as compared to our study.

PMS involves altered activity of the sympathetic nervous system in the late luteal phase of the menstrual cycle. Various studies show that sympathetic functions are altered in PMS and our study suggests the same. Matsumoto found that the ANS activity in the follicular phase did not differ among the subjects regardless of their premenstrual symptoms[16] Girdler et al.,[19] revealed that women with PMS had significantly elevated norepinephrine and total peripheral resistance during both phases as compared with control subjects. Although most studies do not comment on the follicular phase, the present work demonstrated insignificantly higher basal sympathetic activity in the PMS group than the control group during the follicular phase (P>0.05) as per (Table 2). Ozisik et al., observed no statistical difference in the sympathetic response during the luteal phase between the PMS patients and the control group.[20] Assoc and Magos investigated that the patient's premenstrual distress appeared to arise mainly

from chronically high autonomic activity.[4] Koeske found a premenstrual increase in skin conductance, a test to measure the sympathetic axis.[21] Matsumoto found that women with PMS exhibit high sympathetic activity during the luteal phase.[19] Despite the differences in experimental designs and conditions, earlier investigations[4,19,21] are in coherence with our findings, indicating that the occurrence of premenstrual symptomatology could be attributable to the uplifted sympathetic axis in the symptomatic late luteal phase. During the luteal phase, there was a significant increase in sympathetic activity in the PMS group as compared to the control group ($P<0.001$) (Table 3). Stress in any form is associated with an increase in HR and BP reflecting an uplifted sympathetic axis. It is conceivable that increased sympathetic functions in the luteal phase are associated with the cluster of symptoms appearing premenstrually. Moreover, PMS has a multicausal origin; a definite etiopathological cause remains elusive and needs further investigations.

A study of the classification of sympathetic functions into normal, borderline, and abnormal is according to Ewing's criteria. About 54% of cases showed a normal range in comparison to 56% abnormal results in HGT. OHT showed 79% in the normal range. The mechanisms by which cardiac autonomic function among PMS females may be affected involve psychoneuroendocrinal pathways. Altered activity of the hypothalamus-pituitary-adrenal cortex axis and lifestyle factors may contribute to the hyperactive sympathetic system and cluster of symptoms. Prompt identification of these persons will help in early intervention by behavior therapy, relaxation techniques, and pharmacotherapy to prevent long term cardiovascular hazards.

Strength of study

Our study suggests that females with PMS have elevated sympathetic responses. We can identify subclinical autonomic reactivity in PMS patients by doing cardiac autonomic function tests, so persons at risk of developing the cardiovascular disease may be recognized at the earliest and can be treated appropriately to improve their quality of life.

Limitations of the study

Due to time and fiscal constrain, a small sample size was taken which reduced the statistical power of the study to a certain extent. Thus, a study including a greater number of subjects along with a wider age group range is recommended to further assess the sympathetic status.

CONCLUSION

The study results revealed that patients with PMS suffer from an exaggerated sympathetic response state which manifests as the altered response in sympathetic function tests. As PMS involves a psychoneuroendocrinal turmoil, early screening of high-risk groups and implementing interventions such as relaxation techniques and lifestyle modification can prevent further cardiovascular complications in the patients of high sympathetic responses.

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ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Assessment of clinico-radiological and biochemical markers of rickets: A hospital based prospective follow up study

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ABSTRACT

Background: Rickets is a disorder of defective mineralization due to deficiency of calcium and vitamin D and is more prevalent amongst the developing nations. Rickets has been ranked amongst the five most prevalent diseases in children of developing countries. The diagnosis of rickets is based on clinical features, biochemical studies and radiological signs and confirmed by response to treatment. **Aims and Objectives:** The purpose of this study is to evaluate the clinical, radiological and biochemical markers of the rickets by measuring the markers at the time of presentation, at 6 weekly intervals and after completion of treatment with standard regimen for rickets. **Materials and Methods:** 101 cases of nutritional rickets in age group 6 month to 18 years were allocated to receive combination therapy of calcium and vitamin-D according to their age and weight during a study period of 24 weeks. Radiographs (wrist and knee) and biochemical parameters (serum calcium, inorganic phosphate, alkaline phosphatase [ALP], and Vitamin-D), as well as clinical features, were evaluated at presentation, 6, 12, 18, and 24 weeks and response of treatment and markers were assessed at subsequent interval. clinical, radiological, biochemical parameters were evaluated statistically with Chi-square test for qualitative and 2 or more different variables by ANOVAs respectively. A $P<0.05$ was considered statistically significant analysis was done using Statistical Package for Social Sciences version 21.0. **Results:** At presentation, the mean dietary intake of calcium was low in all cases (6.11 ± 0.78 mg/dl). Mean vitamin-D level was (23.05 ± 8.14 ng/ml) indicative of vitamin-D deficiency. At the end of treatment (i.e., 24 weeks) clinical, radiological, and biochemical evidence of healing was observed. Normal serum ALP and complete radiological healing at 12 weeks was observed in 75% of subjects with the improvement of all markers. **Conclusion:** Children with rickets having low dietary calcium intake and low serum Vitamin-D levels have maximum number of markers at presentation. After intervention of combination regimen of calcium and Vitamin-D, remarkable improvement in clinical, radiological, and biochemical markers was found.

Key words: Biochemical markers; Clinico-radiological; Rickets

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INTRODUCTION

Rickets is a disorder of growing children due to defective mineralization of newly formed bone matrix because of Vitamin D deficiency.[1,2] Rickets has been ranked among the five most prevalent diseases in children of developing countries.[3] The diagnosis of rickets is based on clinical features, biochemical studies, and radiological signs and confirmed by response to treatment.[4] Exclusive breastfeeding without Vitamin D supplements for the baby, lack of sunlight exposure, inappropriate dietary intake, and poor housing would contribute to the development of rickets.[5,6]

The clinical signs and symptoms of rickets include bow legs, rachitic rosary, frontal bossing of the skull, widened wrist and ankle joints, and poor growth. Nutritional rickets is biochemically characterized by elevated serum

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alkaline phosphatase (ALP) activity, normal or decreased serum level of calcium and phosphate, secondary hyperparathyroidism, and decreased 25-OHD serum concentrations.[7,8] Radiographic changes of active rickets are evident at growth plate of rapidly growing long bones. These changes reflect expansion of the cartilaginous growth plate and delayed mineralization. The junction of the mineralizing metaphysis with the cartilaginous physis (zone of provisional calcification) increase in longitudinal thickness. Consequently, the luscent gap between metaphysis and epiphysis expands because the shadow of the zone of provisional calcification is partially or totally invisible.[9] The changes occurring in metaphysis may appear to be indistinct, frayed, and irregular on X-ray examinations.[10] Though changes of rickets on radiographs are well characterized, there is no specific method for grading the severity of these changes that has been in general use. Consequently, it is difficult to compare objectively or follow radiographic improvement. To the best of our knowledge, only one study by Thacher *et al.*, was conducted to evaluate the utility and reproducibility of a 10-point scoring method for measuring the severity of rickets.[11]

Aims and objectives

The purpose of this study is to evaluate the clinical, radiological, and biochemical markers of the rickets by measuring the markers at the time of presentation, at 6 weekly intervals, and after completion of treatment with a standard regimen for rickets.

MATERIALS AND METHODS

The study was conducted in the Department of Orthopaedics at our institution. The patients were followed up in the outpatient department on the basis of the provided visit. The clinical features, biochemical changes, and radiological findings were noted at every follow-up visit.

Inclusion criteria

The study included all children of nutritional rickets of age 6 months to 18 years, as well as patients presenting with recurrent LRTI, delayed milestones, diarrhea, or increase bone fractures.

Exclusion criteria

The patients of primary rickets associated with other comorbidities, major congenital malformations, chromosomal abnormalities, or any other metabolic disorders as well as patients of secondary rickets were excluded.

Intervention

Children of rickets were treated with calcium and vitamin D regime (Age 6–12 month with Vitamin D (IU/ DL) - Single dose of 50,000, Daily dose × 12 weeks of 2000, Maintenance dose × 24 weeks of 400, with Calcium 300–400 mg/dl/day.

Age 1–12 years with Vitamin D (IU/DL) - Single dose of 1,50,000, Daily dose×12 weeks of of 3,000–6,000, Maintenance dose×24 weeks of 600, with Calcium 600–1,200 mg/dl/day.

Age >12 years with Vitamin D(IU/DL) - Single dose of 3 Lacs, Daily dose×12 weeks of 6000, Maintenance dose×24 weeks of 600 with Calcium 1300– 1500 mg/dl day). In the follow-up visits, their serum biochemical markers and X-rays of wrist and knee were taken. Radiological markers were noted and the number of remaining clinical markers in the consecutive visits were noted.

Outcome measures

The following eight chief clinical parameters were used 1) Craniotabes 2) Harrison's sulcus 3) Rachitic changes 4) Widening of the wrist and knee 5) Bowing and Knock-knee 6) Pigeon chest 7) Joint swelling and tenderness 8) Difficulty in walking. Seven chief radiological parameters were 1) Epiphyseal enlargement 2) Splaying, fraying, and cupping 3) Rachitic rosary 4) Loss of provisional zone of calcification 5) Periosteal thickening 6) Pathological fracture 7) Coxa vara/valga. Biochemical markers were 1) serum calcium 2) serum phosphate 3) serum ALP 4) serum Vitamin-D. Each patient of rickets was followed up at 6 weekly interval and their clinical, radiological, and biochemical markers were assessed primarily at the time of presentation of the cases and then again at each follow up visit upto 24 weeks. The outcomes and overall improvement in all three markers were compared at the end of study period.

Ethics

Since the study involves human subjects, procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional). Institutional Ethical Committee approval was taken for this study.

Statistical analysis

Improvement in clinical, radiological, and biochemical parameters were evaluated statistically with Chi-square and ANOVA tests. A $P<0.05$ was considered statistically significant. The data were analyzed using Statistical Package for Social Sciences version 21.0. Biochemical markers and anteroposterior and lateral radiographs were taken at every visit for comparison of the radiological markers with clinical markers.

RESULTS

The study consisted of a total 101 cases who were clinically diagnosed and further confirmation by radiograph and biochemical investigations was done. Among the study population, 57 were male and 48 were female. About 27.73% cases were in the age group of 6 months to 1 year, 33.66% were in the age group of 1–6 years, 27.72% were 6–12 years and 11.88% cases were present in the age group of 12–18 years. The mean age was 5 years. 68 cases were from rural area and 43 cases from urban area. Among these, 15 cases belonged to the upper class, 26 to the middle class and 60 cases belonged to lower socioeconomic status. Prevalence among males is more and mostly found in rural communities belonging to lower socioeconomic status.

A total of eight clinical markers relevant to the general population were taken in the study. Five cases had craniotabes with frontal bossing, 7 had Harrison's sulcus, rachitic changes in the ribs were seen in 29 patients, widening of wrist and knee in 18 patients, bowing of lower limb in 34 patients, knock knee in 31 patients, pigeon chest deformity in 4, three patients had difficulty in walking while joint swelling and tenderness was seen in 27 patients. Apart from these, some patients presented with more than one clinical marker with non-osseous features such as potbelly. Malnutrition with poor development, growth retardation, dental defect, and muscle weakness were also present (Table 1).

Earliest sign of clinical relief is pain and bony tenderness while delayed response is in the deformity of the lower limb. Signs of clinical relief were found after 6 weeks of treatment. Other associated symptoms returned to the normal range within 4 to 6 weeks. Some patients (6.68%) did not respond, for whom Vitamin D therapy with 3 lac or 6 lac IU was given monthly, intramuscularly and symptoms were relieved. The patients with lower limb deformity such as genu valgum and genu varum which did not correct spontaneously were advised to undergo corrective osteotomy.

There was a total of seven parameters for assessment of radiological markers, and they were epiphyseal enlargement (34 cases), features of splaying fraying and cupping (78 cases), rachitic rosary (22 cases), loss of provisional zone of calcification (57 cases), periosteal thickening (41 cases), pathological fractures (2 cases) and coxa vara (1)/coxa valga (2). Apart from these, most of these patients had widening of epiphysis and metaphysis (Figures 1 and 2). After a period of 24 weeks, 85.5%cases showed radiological healing while the rest did not respond with the regime. Vitamin-D levels

Table 1: Association between number of clinical markers with time interval

N=101	Number of cases present						
Clinical markers (n=8)	At presentation	6 weeks	12 weeks	18 weeks	24 weeks	Total	Chi-square test
8	10	4	2	1	0	17	χ^2=245
7	8	3	1	0	0	12	Diff=32
6	7	3	2	1	0	13	P<0.001
5	13	6	3	2	0	24	(Highly significant)
4	16	25	14	17	5	77	
3	20	28	30	20	7	105	
2	24	20	22	16	18	100	
1	2	11	24	36	32	106	
0	1	1	3	7	39	51	

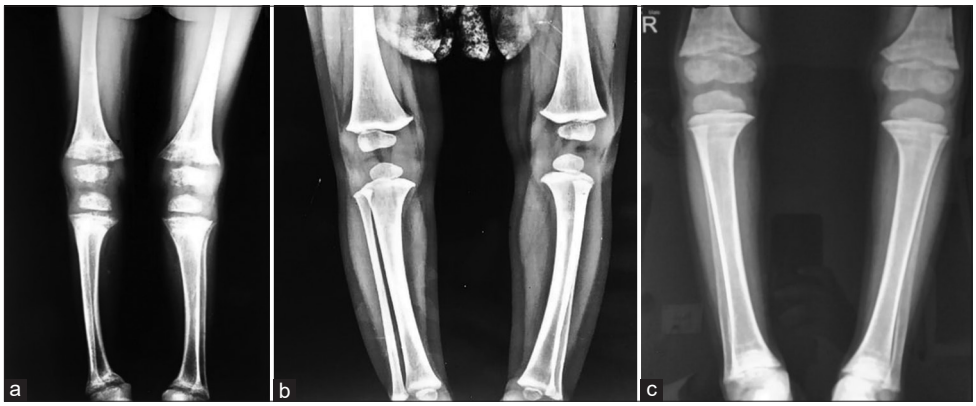

Figure 1: (a) At presentation, (b) at 6 weeks, (c) at 12 weeks

are directly correlated with the severity of rickets. At presentation, 22 cases had <30 nmol/l Vitamin-D and more radiological markers. At the end of 6 weeks, when all biochemical parameters started increasing towards the normal level, radiological markers started healing. Serum ALP most closely related to the severity to the radiological rickets (Table 2).

There were 4 biochemical parameters which were taken into account in our study. These were serum calcium, serum phosphate, serum ALP, and serum vitamin-D_3. Other markers such as serum PTH and serum cholesterol were not taken as they were costlier investigations and were not feasible for most patients. Serum calcium levels were at significantly lower levels at the time of presentation (mean value 6.08 mg/dl) and serum phosphate level (mean value 3.99 mg/dl) was also low. Both values started rising on treatment with standard regimen of rickets. After 6 weeks on 1st follow-up, serum calcium and serum phosphate values came near-normal range, and after 18 weeks, their mean values became normal i.e. 8.05 mg/dl and 5.08 mg/dl. Serum ALP levels at the time of presentation (mean value 651 IU/L) were significantly higher than the normal value (44–115 IU/L). Serum ALP closely related with severity of the rickets. During the course of the study, serum ALP levels followed a gradual pattern of fall, with a mean starting value during the first OPD visit of 651 IU/L, 582 IU/L at 6 weeks, 447 IU/L at 12 weeks, 361.61 IU/L at 18 weeks, and coming to normal range (115.73) after 24 weeks of treatment (Table 3).

Clinical, radiological, and biochemical markers which were resolved at the end of follow up (24weeks) interpreted as follows – clinical 93.327%, radiological 85.55%, biochemical 98.44% while those Not resolved are as follows – clinical 6.68%, radiological 14.1%, biochemical 5.66%. χ^2=2.97, P<0.05 (Significant).

Radiological findings

Improvement in the calcification around the knee in Figure 1 and around wrist after vitamin D administration.

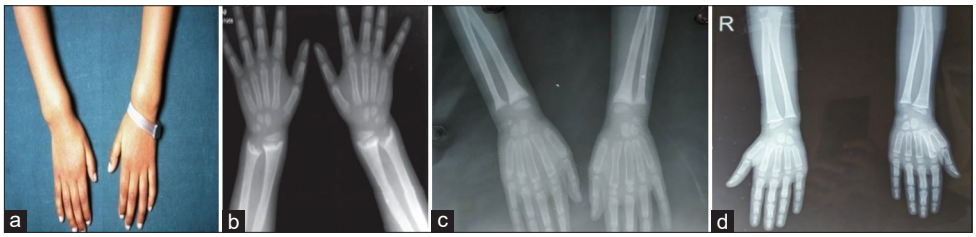

Figure 2: (a and b) At presentation, (c) at 6 weeks, (d) at 12 weeks

Table 2: Association between the number of radiological markers in study population with time interval

N=101	Number of cases present					Total	Chi-square test
	Pre-treatment	Post-treatment					
Radiological markers (n=7)	At presentation	6 weeks	12 weeks	18 weeks	24 weeks		
7	26	15	8	5	3	57	χ^2=249.60
6	22	18	10	3	1	54	Diff=28
5	20	24	10	4	2	60	P<0.001
4	10	13	22	9	3	60	(Highly significant)
3	10	14	28	14	9	75	
2	5	5	15	29	22	76	
1	7	6	3	23	35	74	
0	1	3	5	14	26	49	
Total	101	101	101	101	101		

Table 3: Mean values of biochemical markers with response of treatment

Serum biochemical markers (n=101)	Pre-treatment values	Mean value of serum markers during treatment				P value
	At presentation (Mean±SD)	6 weeks (Mean±SD)	12 weeks (Mean±SD)	18 weeks (Mean±SD)	24 weeks (Mean±SD)	
Calcium (mg/dl)	6.11±0.78	7.05±0.68	7.23±2.75	8.05±0.93	9.42±0.68	<0.001
Phosphate (mg/dl)	3.99±0.58	4.35±0.69	4.51±0.54	5.08±0.72	5.33±0.71	<0.001
Alkaline phosphatase (iu/l)	651±242.1	582.96±203.41	447.34±95.82	361.6±107.42	115.73±44.77	<0.001
Vitamin-D_3 (mmol/l)	23.05±8.14	38.85±8.40	76.83±16.23	78.31±15.6	94.63±9.70	<0.001

DISCUSSION

Rickets remains a major public health problem in developing countries like India. The etiopathogenesis of rickets is thought to be multifactorial, for example, lack of exposure to sunlight, prolonged breastfeeding, multiple pregnancies, and lack of supplementation of food rich in Vitamin D. The relationship between Vitamin D and feeding pattern, duration of breastfeeding, age of complementary feeding, children and mother selective type of food, number of deliveries, sun exposure, clothing, and house type were also assessed. Nevertheless, the age at which to introduce complementary feeding, duration of complementary feeding, appropriate frequency of feeding, content, and factors affecting intake of complementary foods are beyond the scope of the current study and require further study.

In our study, genu-varum deformity was most common. Other features such as beading of the rib cage, Harrison's sulcus, bony tenderness at wrist and knee were other common features. Many studies showed that lack of sunlight increases the risk of rickets.[12] In general, the distribution of rickets among children was decreased with increasing exposure frequency to sunlight. The more the child was exposed to sunlight, the more was the production of vitamin D in the skin. This result is consistent with other studies.[13] Mothers, who sought advice from both doctors and mother and child-care workers, were found to have the lowest number of rachitic children.[14]

In addition to the clinical features, the rachitic children also demonstrated biochemical alterations. There was significant decrease in the mean values of serum Vitamin D, serum calcium, and serum phosphate levels. In contrast, serum ALP levels were significantly increased in rachitic children. The serum concentration of 25-OH Vitamin $D_3$is an accepted index of Vitamin D nutritional status and should be restricted to the assessment of Vitamin D status.[15]

The first sign of response to therapy is the appearance of healing line of rickets - a radio-opaque line in the epiphysis signifying mineralization of provisional zone of calcification has begun, Dimitri followed his patients 6 weekly to see the response of treatment.[16] In our study, healing line appears after 6 weeks, 46.5% recovered within 12 weeks, and 88.14% by 6 months. In our study, the mean time taken to radiological resolution is 5 months. Radiography in each visit helps to evaluate the response of healing of rickets.

Radiologically, more severe rickets took more time to resolve. Calcium along with vitamin-D_3 leads to quicker resolution of radiological findings.[17] Patients who were not responding to usual regimen of rickets were given Stoss therapy and most of them had resolution within 6 months.

Limitations of the study

Our study was limited due to small sample size and difficulty in follow up of patients due to corona pandemic.

CONCLUSION

All the three parameters clinical, radiological, and biochemical are required to evaluate the outcome measures in rickets patients.

What is known

Distal ends of radius and ulna were used as the radiological indicator for diagnosis and follow-up in nutritional rickets, whereas the distal femur was a better radiological indicator. Thacher's 10-point scoring system is a very useful tool and the only system for assessing the severity and grading radiological changes of nutritional rickets and its follow-up that aids in monitoring improvement.

What this study adds

Non-osseous clinical markers and osseous radiological markers of rickets improved within a month in cases who presented at an early age. Serum ALP was closely related to the severity of the disease and serum vitamin-D level related to the prognosis and outcome of the disease. All the three parameters clinical, radiological, and biochemical are required to evaluate the outcome measures in rickets patients.

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A study on evaluation of knee osteoarthritis with MRI and comparing it with CT scan, high resolution USG and conventional radiography

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ABSTRACT

Background: Knee osteo-arthritis is widely prevalent in the elderly population in our society and associated with significant morbidity and poor quality of life. Early diagnosis of the condition can enable timely and proper care for the patients. Magnetic Resonance Imaging, CT Scan, Ultrasonography and plain radiography are the different modalities of imaging that are commonly used for detection and diagnosis of knee osteo-arthritis. **Aims and Objectives:** To find out the early osteoarthritic changes of knee by Magnetic Resonance Imaging and compare those findings with conventional radiography, high frequency USG and CT scan findings. **Materials and Methods:** Patients suffering from knee osteoarthritis (OA) as per American College of Rheumatology guideline criteria (n = 56) underwent imaging of the knee using plain radiography, ultrasonography, CT scan and MRI. The imaging findings studied in the patients were joint space narrowing (JSN), meniscal abnormality, Baker's cyst, cruciate ligament abnormality, knee effusion, subchondral cyst, and loose bodies. A comparison between radiography, CT scan and USG was done for the imaging findings with MRI as the reference standard. Z-test of proportionality was used to find statistically significant difference for the three imaging modalities. A $P < 0.05$ was deemed statistically significant. **Results:** The mean age of the patients was 61 years (38 males). The tibiofemoral compartment was most commonly affected. CT scan was more sensitive than radiography in detecting subchondral cyst ($P = 0.018$) and loose bodies ($P = 0.004$). USG and MRI were equally sensitive in detecting knee effusion ($P = 0.22$) and synovial thickening ($P = 0.10$). CT scan and MRI were equally sensitive in detecting subchondral cyst ($P = 1.00$) and loose bodies ($P = 0.22$). **Conclusion:** While CT imaging was more sensitive for detection of subchondral cysts and loose bodies than conventional radiography, it was as sensitive as MRI in detecting these findings in the study group. Additional study is warranted to assess diagnostic performance of CT scan and MRI in the diagnosis and progression of knee OA.

Key words: Knee osteoarthritis; Magnetic resonance imaging; Ultrasonography; Radiography

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INTRODUCTION

Osteoarthritis (OA) is a widely prevalent musculoskeletal disease in Indian adults, resulting in significant morbidity in life. The disease is also a considerable economic burden on the health care resources of the country.[1] The knee is the weight-bearing joint of the body and most commonly affected joint in OA. Because of the high prevalence of knee OA, the diagnosis of the same requires improved and simple modalities of imaging.[2] Conventional radiography is widely used as the initial imaging for knee OA but lacks accuracy and precision compared to CT scan and Magnetic Resonance Imaging (MRI).[3] The reason is radiography employs two dimensional projection of the knee anatomy which impedes detailed visualization of the different structures

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causing discrepancies in interpretation. For example, subchondral cysts are a common finding in knee OA, but plain radiographs often fail to detect this feature. Similarly, osteophytes may be missed in plain radiography resulting in significant delay in diagnosis and therefore initiation of treatment. MRI and CT scan are newer imaging modalities which have considerable higher sensitivity and specificity as compared to plain radiography. It also allows better visualization of the tibiofemoral (TF) and patella-femoral compartments of the knee joint. Ultrasonography of the knee joint cavity is also used to ascertain the thickening of the synovial membrane and presence of knee effusion.[4] In the present study, we have studied the imaging features of knee osteo-arthritis using all the four imaging modalities. We compared the finding in knee OA between plain radiography and CT scan with MRI as the reference standard.

Aims and objectives

To find out the early osteoarthritic changes of knee by and compare those findings with conventional radiography, high frequency USG and CT scan findings.

MATERIALS AND METHODS

Study design and ethical approval

The study design is a cross-sectional descriptive study conducted in the Department of Radiodiagnosis and Department of Physical Medicine and Rehabilitation of North Bengal Medical College and Hospital for a period of 1 year. A topic was selected with the title of "A study on evaluation of knee OA with MRI and comparing it with CT scan, high resolution USG and conventional radiography" and first a protocol was formed, and it was submitted to the institutional ethics committee for ethical permission. After ethical permission, a proforma was made and it was pretested and then a final proforma prepared. After taking informed consent, the patients with knee pain diagnosed clinically as OA and referred to the department of Radiodiagnosis for imaging were examined using proper ACR clinical guideline. Then, these screened patients, who fulfill the inclusion and exclusion criteria, were evaluated with MRI, followed by conventional radiography, high frequency USG and CT scan.

Study population

This study was conducted among the patients who were referred to the Department of Radiodiagnosis for imaging with clinical features of knee OA fulfilling inclusion and exclusion criteria.

Inclusion criteria

Clinical features of knee OA as per American College of Rheumatology (ACR) guideline as mentioned afterwards.

Exclusion criteria

a) Patients with knee pain not fulfilling ACR guideline criteria.
b) Patients with specific medical and/or surgical conditions which may involve the knee joint, such as tumor, recent injury, septic arthritis, and operated knee.
c) Patients suffering from other forms of arthritis such as Rheumatoid arthritis, seronegative arthritis, and depositional arthritis.
d) Patients with contraindication for doing MRI.
e) Patients not giving consent for study.

Clinical features for diagnosis of knee OA (as per ACR guideline)

a) Knee joint pain, with 3 other criteria among mentioned criteria below.
b) Age: >50.
c) Morning stiffness lasting for <30 min.
d) Crepitation or grating sensation on active movement.
e) Bony tenderness of knee joint.
f) Palpable bony enlargement around knee joint.
g) No detectable warmth of the joint to touch.

Sample size and sampling technique

Total 56 patients were studied using purposive sampling technique for selection of the patients

Study tools

a) Predesigned, Pretested, Semi structured proforma.
b) Patient's records and registered.
c) High power X-ray machines (300 mA, 500 mA and 800 mA).
d) High frequency USG machine with 5–12 MHZ linear transducer in HD-7 model M/S PHILIPS makes.
e) CT scan machine: M/S HITACHI make PRONTO model, single slice spiral CT scan.
f) MRI machine: 1.5 Tesla, M/S GE make, Bravo model.

RESULTS

In this cross sectional descriptive study, total 56 numbers of patients with clinically diagnosed knee OA were studied, in the department of Radiodiagnosis, North Bengal Medical College and Hospital, Darjeeling. All patients were assessed by history taking, clinical examination followed by MRI, conventional radiography, USG and CT-Scan examination. Data of different variables in different modalities were collected. The final analysis for all the variables was done by standard statistical software and results were as follows:

Demographic profile and clinical findings of the patients

The mean age of the patients was 61.13 years. The number of male and female patients was 18 and 38 respectively.

The TF compartment was more frequently and severely affected in OA of knee joint than the patellofemoral (PF) compartment and within TF compartment, medial TF (MTF) compartment was affected more frequently. Bone marrow lesion (BML) was found among 51.78% of patients in this study, and the most common site of BML was in MTF compartment (68.96%). Cruciate ligament abnormality was seen in 13 (23.21%) of study population, among which anterior cruciate ligament abnormality was seen more frequently 12.5% cases and posterior cruciate ligament in 10.7% cases. Collateral ligament involvement was seen rarely, only in two (3.56%) patients out of 56 patients in this study. Meniscal abnormality in the form of degeneration was found in 21 (37.5%) patients and among these patients medial meniscus was involved in 12 (21.42%) patients and lateral meniscus was involved in 9 (16.07%) patients. Osteophyte was detected in 92.85% patients with conventional radiography but in 100% patients with CT scan and MRI. In all modality in our study, most frequent site of osteophytosis was MTF compartment. In 85.71%, 96.42% and 96.42% of patient, osteophytes was identified in MTF compartment in conventional radiography, CT scan and MRI respectively.

Comparison of USG, CT scan and MRI imaging findings

The imaging findings studied in the patients were JSN, meniscal abnormality, Baker's cyst, cruciate ligament abnormality, knee effusion, subchondral cyst and loose bodies. A comparison between radiography and CT scan was done for JSN, subchondral cyst and loose bodies (Table 1). Similarly, a comparison was done between USG and MRI for detection of knee effusion and synovial thickening (Table 2). Finally, CT scan and MRI were compared for the detection of subchondral cysts and loose bodies (Table 3).

Table 1: Difference in imaging findings between plain radiography and CT Scan. Z test of proportionality was used to test statistical significant difference between the two modalities of imaging

Imaging finding	Radiography	CT scan	P value
Joint space narrowing	36/56	28/56	0.12
Sub-chondral cyst	24/56	36/56	0.018
Loose bodies	08/56	21/56	0.004

Table 2: Difference in imaging findings between USG and MRI. Z test of proportionality was used to test statistical significant difference between the two modalities of imaging

Imaging finding	USG	MRI	P value
Knee effusion	44/56	48/56	0.22
Synovial thickening	37/56	44/56	0.10

Table 3: Difference in imaging findings between CT Scan and MRI. Z test of proportionality was used to test statistical significant difference between the two modalities of imaging

Imaging finding	CT Scan	MRI	P value
Sub-chondral cyst	36/56	36/56	1.00
Loose bodies	21/56	15/56	0.22

DISCUSSION

Early diagnosis and specific measures is the only way to reduce disability from this crippling disease.[5] MRI, though very sensitive for early detection of OA, cost is limiting factor. In other modality like conventional radiography, high frequency USG and CT scan, though cost is low, but all the early osteoarthritic changes are not detected by any of this modality alone.[6]

This cross-sectional observational study was undertaken to evaluate knee OA with MRI and then compare those findings with conventional radiography, CT scan and high frequency USG findings.

Fifty six patients were included in the study and their detailed demographic, clinical and imaging parameters were assessed. Maximum numbers of patients were female and maximum numbers of study population were above 60 yrs of age. All the patients were having symptomatic knee OA. MTF compartment was most frequently affected among three knee compartments. Only MRI detectable changes were cartilaginous defect, BML, meniscal abnormality and cruciate ligament changes in addition to other changes detectable by other modalities.

Cartilage change was seen in approximately one-third case. BML, JSN, osteophytosis, subchondral sclerosis, and subchondral cyst were predominantly seen in MTF compartment.

Significant difference was seen between conventional radiography and CT scan in the detection of loose bodies and subchondral cyst (P-value 0.004 and 0.018 respectively). Loose body and subchondral cyst was better detected on CT scan than radiograph. Detection rate of subchondral cyst on CT scan and on MRI is equal, so relation of Radiography with MRI in detection of subchondral cyst is similar to relation with CT scan, which is significant.

No significant difference was found between conventional radiography and CT scan for detection of JSN and osteophytes (P-value 0.09 and 0.06 respectively). Osteophytes in the different compartments of the knee joint were detected

both on CT scan and MRI in similar frequency. Subchondral sclerosis was equally detected on conventional radiography, CT scan, and MRI. Moreover, no significant difference was found between high frequency USG and MRI for the detection of joint effusion, synovial thickening (P-value 0.22 and 0.10 respectively). High frequency USG and MRI were almost equally effective for detection of Baker's cyst.

The present study was carried out over a period of 1 year on 56 numbers of patients with clinically diagnosed knee OA, in the Department of Radiodiagnosis, NBMCH, Darjeeling with the aim to find out the osteoarthritic changes of knee by MRI and compare those findings with conventional radiography, high frequency USG and CT scan findings.

In our study, the TF compartment was more frequently and severely affected in OA of knee joint than the PF compartment and within TF compartment, MTF compartment was affected more frequently.

In this study, MRI was a unique modality for detection of cartilage defect, BML, meniscal lesion, ligamentous lesion; no other modality could detect the changes in OA of the mentioned structures.

In the present study, articular cartilage defect on MRI was found in 41 (73.21%) patients, while in a study Joshi et al., found articular cartilage defect in almost every patient. Foo et al., in their study found articular cartilage defect in 37.1% of the patients.[7] However Bruyère et al., in their study reported articular cartilage defect in 75% patients, which is very close to our study result.[8]

BML was found among 51.78% of patients in this study and the most common site of BML was in MTF compartment (68.96%). Bruyère et al., in their study reported BML in 57% patients.[8] Bacon et al. in their study found BML in 46.9% of knee joint and Fernandez-Madrid et al., found BML in 65% of the patients.[9]

Meniscal abnormality in the form of degeneration was found in 21 (37.5%) patients and among these patients medial meniscus was involved in 12(21.42%) patients and lateral meniscus was involved in 9 (16.07%) patients. Bruyère et al., in their study found meniscal abnormality in 27% of the study population.[8]

Cruciate ligament abnormality was seen in 13 (23.21%) of study population, among which anterior cruciate ligament abnormality was seen more frequently 12.5% cases and posterior cruciate ligament in 10.7% cases. Collateral ligament involvement was seen rarely, only in two (3.56%) patients out of 56 patients in this study. Joshi et al., was found ACL and PCL involvement in 25% and 34.7% respectively. No tendon abnormality was found in any of the study population.

JSN was found in 64.28% and 50% patients in conventional radiography and in CT scan respectively and in both of this study, MTF compartment involvement was seen more frequently. The probable reason behind it is that JSN on conventional radiography is seen in weight bearing AP view, in which very minute amount narrowing can be detected accurately, where as on CT scan, JSN is seen in scanogram or in reformatted coronal image, which is taken in supine position; so JSN could not be measured accurately.[10]

Osteophyte was detected in 92.85% patients with conventional radiography but in 100% patients with CT scan and MRI. In all modality in our study, most frequent site of osteophytosis was MTF compartment. In 85.71%, 96.42% and 96.42% of patient, osteophytes was identified in MTF compartment in conventional radiography, CT scan and MRI respectively. Ai et al., reported osteophytes in 100% of the knee affected by OA on MRI.[11] Chan et al., in their study found that in the medial compartment CT and MRI showed osteophytes in 100% of the knee where as radiography showed osteophytes in only 60% of the cases.[12] In this study, no significant difference was found between CT scan and MRI in the detection of osteophytes. So, for only detection of osteophyte CT scan and MRI will be supplementary to each other.

Subchondral sclerosis was equally detected on conventional radiography, CT scan, and MRI and it was seen in 71.42% of study population and predominantly seen in MTF compartment. Bruyère et al., reported subchondral sclerosis in 43% of patients.[8] So, conventional radiography will be supplementary to CT scan and MRI for the detection of subchondral sclerosis.[13]

Subchondral cyst was found in 24(42.85%), 36 (64.28%) and 36 (64.28%) of the study population on conventional radiography, CT scan and MRI respectively and with all modality subchondral cyst was maximally detected in MTF compartment. Wu et al., in their study found subchondral cysts in 50% of patients on MRI.[14] In this present study, no difference was seen between CT scan and MRI in the detection of subchondral cyst but significant difference was seen between conventional radiography and CT scan, and conventional radiography and MRI. Low detection rate of the subchondral cyst on conventional radiography is possibly due to obscuration of small cyst in deeper part of condyles by the impression of overlapping thick bone on two dimensional radiographic film.[15]

Loose body was found in 21(37.5%), 15(26.78%) and 8 (14.28%) of patients on CT scan, MRI and conventional radiography respectively. There was a significant difference

between CT scan and two other modalities like MRI and conventional radiography, in the detection of loose body. In this study, CT scan was the best modality for the detection of loose bodies.

Knee effusion was seen on USG and MRI in 78.57% and 85.71% of study population respectively. Fernandez-Madrid et al., in their study found knee effusion in 60% of patients on MRI.[16] Tarhan and Unlu in a study reported knee effusion in 70% and 85% of patients on USG and MRI respectively, which is almost similar to the result of the present study.[17]

In this study, synovial thickening was detected more commonly on MRI than USG and on USG and MRI synovial thickening was seen in 66.07% and 78.57% of the cases respectively. This difference was probably due to the fact that, on MRI synovial thickening was seen in multiple locations where as on USG synovial thickening was seen only in suprapatellar pouch region;[18] So, on USG we may missed the synovial thickening in the region other than suprapatellar pouch of knee, which are easily seen on MRI. Tarhan-Unlu et al., reported in their study that, synovial thickening was seen in 73% case of study population on MRI.[17] Tarhan and Unlu in their study found synovial thickening in 34% and 50% of cases on USG and MRI respectively and MRI was superior modality than USG in the detection of synovial thickening, similar to this present study.

Baker's cyst was seen in 25 (44.64%) cases of study population and the incidence of detection of Baker's cyst with USG and MRI were same. Hall et al., in their study found baker's cyst in 39% of study population which is nearer to this study result.[19] Joshi et al., found baker cyst in 40.63% of the patients.[20] Where as Tarhan and Unlu found baker cyst in 40% and 35% of cases on USG and MRI respectively.[17]

Limitations of the study

- In this study, the cartilage thickness measurement using high frequency USG was not done in our study set-up, due some technical problem.
- In this study cartilage changes on MRI was assessed only qualitatively, no quantitative assessment was done.
- In this study non contrast MRI of knee was done, no contrast enhanced MRI done, so there is chance of missing actual number of case even with minimal synovial thickening.

CONCLUSION

MRI is unique modality for detection of articular cartilage destruction, even if it is very minimal (earliest change), BML, meniscal abnormality and cruciate ligament abnormality. However, in this present study, among those MRI findings which are comparable with the findings of other three modalities, MRI was seen superior to conventional radiography for the detection of subchondral cyst but in that respect it was seen equally effective with CT scan. So, though MRI is costly, not always available and not feasible for every patient, in this modern era, when disease modifying drugs are available and early diagnosis may change the disease progression, MRI is the best modality for early detection of OA changes of the knee joint. However, for follow-up MRI or any one of the other three modalities can be used alone or in combination, which will detect almost all changes of advanced OA and will reduce cost to the patients and will be readily available to every patient.

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RS- Concept and design of the study, prepared first draft of manuscript; **CKD-** Interpreted the results; reviewed the literature and manuscript preparation; **DS-** Concept, coordination, statistical analysis and interpretation, preparation of manuscript and revision of the manuscript

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Risk of kidney health among returnee Nepali migrant workers: A survey of nephrologists

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ABSTRACT

Background: Anecdotal reports suggest an increasing prevalence of kidney problems in returnee Nepali migrant workers from the Gulf countries and Malaysia. **Aims and Objectives:** This study aims to (a) explore the magnitude of the kidney health-related problems in returnee Nepali migrant workers; and, (b) assess the need for further scientific investigations. **Materials and Methods:** This was a self-administered survey of practicing nephrologists in Nepal. All 51 nephrologists working in Nepal (at the time of this study) were approached by email for anonymous participation using an online survey platform. Data were collected between December 2019 and February 2020. Descriptive statistics were generated for data analysis. **Results:** A total of 38 nephrologists completed the survey. Almost all their migrant patients were: younger than 40 years, males, from rural areas of Nepal, and had worked in Gulf countries or Malaysia. Most (92.1%) of the respondents reported that the causes behind kidney-related problems of returnee migrant workers were of unknown etiology and less likely to be linked to traditional risk factors. Chronic kidney disease and glomerulonephritis were the most common kidney health-related problems. The vast majority of respondents (76.3%) thought that the returnee migrant workers are at a higher risk of kidney-related problems than the general Nepali population. **Conclusion:** Nepali labor migrants in the countries of the Gulf and Malaysia could be at a higher risk of kidney health-related problems than the general Nepali population. Further rigorous scientific investigation is warranted to examine the kidney-health-related risk of Nepali migrant workers.

Key words: Acute kidney injury; Chronic kidney disease; Glomerulonephritis; Kidney failure; Kidney health; Migrants; Nepal

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INTRODUCTION

The burden of chronic kidney disease (CKD) related morbidity and mortality is slowly rising.[1,2] A systematic review estimated the global prevalence of CKD between 11% and 13%[3] with estimated annual mortality due to kidney disease between 5 and 10 million.[4] Due to the lack of a national registry system, it is difficult to ascertain the prevalence of CKD in Nepal. However, a recent nation-wide cross-sectional survey in Nepal among 12,109 participants (aged 20 years or over) estimated the prevalence of CKD at 6.5% for men and 5.7% for women.[5] A community-based study in Eastern Nepal estimated the prevalence of 10.6% among population aged 20 years or above,[6] most common causes of which are chronic glomerulonephritis (CGN), diabetes mellitus, and hypertension.[7]

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Labor migration is an inevitable livelihood option for thousands of Nepali and more than 4 million work permits have been granted since 2008/2009 for work-related international migration to countries other than India.[8] Citizens of Nepal and India do not require a labor permit to work in each other's country. The most recent Nepal Demographic and Health Survey 2016 showed that 47% of the Nepali households had at least one migrant member in the family in the last decade.[9] According to the Nepal Labor Migration Report 2020, Nepali labor migrants are mostly males, low-skilled, the vast majority work in Gulf Cooperation Council (GCC) countries and Malaysia and had sent over US$ 8.8 billion of remittance home in the year 2018/19.[8]

Nepali media often report a high prevalence of kidney failure in returnee Nepali migrant workers from GCC and Malaysia.[10,11] It is unknown if these higher rates of kidney health-related problems are due to the natural rise in number in a country with a huge number of the population migrated for work or whether there is an increased risk compared to the general Nepali population due to the working and living conditions in abroad. Medical treatment of kidney health-related problems in Nepal is limited and expensive, especially in end-stage renal disease, where renal replacement therapies in the form of dialysis or renal transplantation are the only specific measures of management. This has huge financial implication to their family and could push them towards poverty.

In the recent years, the evidence is emerging that chronic or repeated episodes of heat stress accompanied by strenuous work and dehydration may trigger pre-renal acute kidney injury (AKI) that might eventually progress to CKD.[12] This phenomenon has been mainly attributed to disproportionately higher CKD rates in agriculture workers in Central America, America, India, Sri Lanka, Thailand, and in other countries.[13] The vast majority of migrant workers in the countries of the Gulf and Malaysia work in searing heat with intense physical exertion with less opportunity of regular rehydration.[14] Thus, we speculate that this working condition may expose them to a higher risk of kidney injuries and subsequent CKD.

There is no reporting system to understand the health issues of returnee migrants in Nepal nor do hospitals keep a record of their patients by migrant status. Though many studies among Nepali migrants report wide-ranging health and wellbeing issues,[15,16] none of them reported the kidney health-related problems while abroad or after their return.

Aims and objectives

This study aims to (a) explore the magnitude of the kidney health-related problems in returnee Nepali migrant workers; and, (b) assess the need for further scientific investigations.

MATERIALS AND METHODS

This was a self-administered online survey among nephrologists of Nepal.

Respondents

The study population was the entire group of nephrologists of Nepal. There were 51 members in the Nepal Society of Nephrology at the time of this study. Inclusion criteria were nephrologists currently practicing in Nepal, had Internet access, and could be contacted through email.

Questionnaire

A questionnaire was developed by study team members based on the literature review and by consulting with migrant and kidney health-related experts (Supplemental 1). It included 23 questions consisting of closed-ended, free-text, and questions with multiple responses. The questions included the socio-demographic characteristics of returnee migrant workers, their major destination countries and occupation, specific kidney-related problems returnee migrants usually have and possible causes, risk of kidney-related problems of returnee migrant compared to general Nepali population, and need for further research. Respondents were asked to provide this information based on their general experience and communication with returnee migrants during medical treatment. A questionnaire was pre-tested[17] among four nephrologists who were excluded from further participation to avoid contamination of the study sample.

Data collection and analysis

The JISC online survey platform (www.onlinesurveys.ac.uk) was used to design the survey contents. The survey weblink and participant information sheet were provided for anonymous participation. Since this was a self-administered online survey, participation in the survey meant providing consent for the study. One of the authors (AS), a practicing Nepali nephrologist, contacted colleagues in Nepal through social media and by email and phone to encourage them to participate in the study. Data were collected between December 2019 and February 2020. Descriptive statistics were generated using the mean, standard deviation (SD), range, frequency, and percentages using STATA software version 14 (Stata Corporation, College Station, TX, USA).

Ethical considerations

Ethical approvals were sought from the Nepal Health Research Council (reference number 1199/2019), a government ethical clearance body for health research in Nepal, and Research Ethics Committee of Bournemouth University (reference number 23986).

RESULTS

A total of 38 nephrologists responded to this online survey. Assuming that the survey has reached to all study population excluding four who participated in a pilot survey (i.e. 47 of 51 nephrologists), the response rate was 80.8%.

Characteristics of respondents

Most respondents (84.2%, n=32) were male, from Kathmandu district, and based in four of the seven provinces of Nepal. They worked as a nephrologist for a minimum of two to a maximum of 34 years. The mean number of patients they saw daily was 22 (SD 11.8, range 10–75). Responding nephrologists reported that of all patients they saw daily, on average 1.7% (SD 2.9, range 0.1–15) were returnee migrant workers and this was highest in Morang district (10%). Table 1 shows the sociodemographic characteristics of responding nephrologists.

Respondents' experience with returnee migrant patients

Almost all their migrant patients were younger than 40 years, male, from rural areas of Nepal, and had worked in GCC countries and Malaysia (Table 2). Twenty-six out of 37 respondents (70.3%) reported that their migrant patients were involved in an outdoor job while abroad, however, they did not know their patients' occupation. Most respondents (68.4%, n=26) reported they did not know if their migrant patients had the kidney problems before they went for employment, however, two (5.3%) reported that proteinuria was diagnosed in migrant patients before they went abroad for work.

Figure 1 shows that CKD and glomerulonephritis were the most common kidney problems of returnee migrant workers according to nephrologists. Most (92.1%, n=35) respondents reported that the causes behind kidney-related problems of returnee migrant workers were of unknown etiology, and the rest related to traditional risk factors (e.g. diabetes, hypertension).

Table 1: Sociodemographic characteristics of the responding nephrologists (N=38)

Continuous variables	Mean (SD)
Age (years)	43.8 (7.2)
Working period as a nephrologist (years)	8.9 (7.4)
Categorical variables	**Number (%)**
Sex	
Male	32 (84.2)
Female	6 (15.8)
Place of practice (district)	
Kathmandu	27 (71.0)
Rupandehi	3 (7.9)
Chitwan	2 (5.3)
Kaski	2 (5.3)
Lalitpur	2 (5.3)
Sunsari	1 (2.6)
Morang	1 (2.6)
Types of health facility	
Private hospital or clinic	11 (28.9)
Public hospital or clinic	5 (13.2)
Both private and public	22 (57.9)

Table 2: Respondents' experience with returnee migrant patients (N=38)

Variables	Number (%)
Most common age group of migrant patients (years)	
20–29	11 (28.9)
30–39	9 (23.7)
20–29 and 30–39	17 (44.7)
20–29, 30–39 and 40–50	1 (2.6)
Most common sex of migrant patients	
Male	37 (97.4)
Male and female equally	1 (2.6)
Most common living areas of migrant patients (in Nepal)	
Rural	29 (76.3)
Urban	7 (18.4)
Do not know	2 (5.3%)
Major work destination of migrant patients*	
Gulf	16 (42.1)
Gulf and Malaysia	16 (42.1)
Gulf, Malaysia, and Korea	4 (10.5)
Gulf, Malaysia, and India or Korea	2 (5.3)
Type of work of migrant patients (N=37)	
Outdoor	26 (70.3)
Indoor	1 (2.7)
Do not know	10 (27.0)
Are migrant patients from a specific ethnicity?	
Yes	0 (0)
No	13 (34.2)
Do not know	25 (65.8)
Are migrant patients with kidney problems have a specific occupation? (n=37)	
Yes	5 (13.5)
No	5 (13.5)
Do not know	27 (73.0)
The kidney problem of migrant patients is prior to working abroad	
Yes	3 (7.9)
No	9 (23.7)
Do not know	26 (68.4)

*More than one response possible

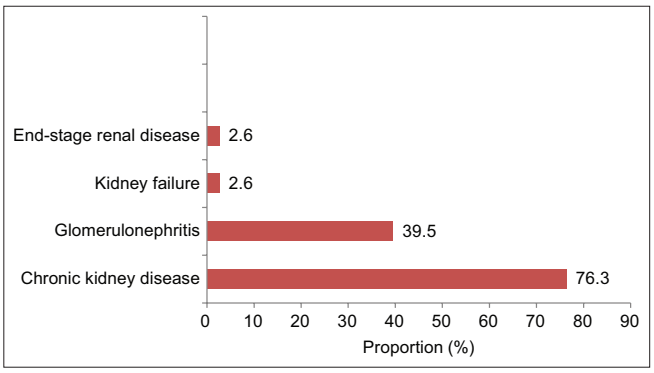

Figure 1: Percentage of kidney problems of returnee labor migrants reported by nephrologists in Nepal (multiple responses possible) (N=38)

Respondents predicted the following possible risk factors for the kidney-related problems on returnee migrant workers:

(i) Dehydration
(ii) Use of salty and fizzy drinks and excessive protein intake (e.g. meat)
(iii) Heavy physical work
(iv) Use of painkillers (non-steroidal anti-inflammatory drugs)
(v) Lack of regular health check-up.

Twenty-three (60.5%) respondents reported that they had ever treated migrant patients who were returned back to Nepal only because of kidney-related problems. On average this number of patients was 7.7 (SD 7.6, range 1–30).

The majority (76.3%, n=29) of respondents thought that the returnee migrant workers are at a higher risk of kidney-related problems than general Nepali population; less than one-quarter (21.1%, n=8) were uncertain and one (2.6%) disagreed. All respondents agreed that kidney health-related problems in returnee Nepali migrant workers warrant further scientific research to understand the magnitude of the problem.

Some important free-text responses from the respondents include:

- Some of the migrant patients are aware that working in GCC countries may damage their kidneys (Respondent 5)
- Needs detailed research in large scales to explore the magnitude of the problem (Respondent 7)
- Need more awareness and better screening before going abroad (Respondent 8)
- Screening of toxins and heavy metals could be important (Respondent 11)
- Nephrologists should be involved in pre-migration health screening (Respondent 15).

DISCUSSION

The present study on Nepal-based nephrologists which is the first of its kind suggests that returnee migrant workers could be at higher risk of kidney-related problems than the general Nepali population. Returnee migrant workers with kidney-related issues were usually male, aged 40 years or below, had worked in GCC countries and Malaysia, and hailed from rural areas of Nepal. The vast majority nephrologists reported that the causes behind the kidney-related problems were of unknown etiology and perhaps less likely to be caused by traditional risk factors (e.g. diabetes, hypertension).

The kidney health risk of low-skilled male migrant workers from Asia in the countries of the GCC and Malaysia are beginning to draw scientific attention.[18] A longitudinal study among Indian construction workers in Saudi Arabia suggested that exposure to heat stress, long working hours, dehydration, sleep deprivation, and obesity may induce the risk to kidney health in workers.[19] In Ponorogo district of Indonesia, 18% of the patients with chronic renal failure were former migrant workers.[20] A qualitative study among Indonesian migrant workers with CKD reported that they were also involved in unhealthy eating, such as a high intake of alcohol and soft drinks and high consumption of fast food.[21] A global systematic review reported that 15% of individuals working in extreme heat had kidney disease and injuries which is significantly higher than that of the general population living in high-income and low-income countries.[22]

In the present study, 92.1% of the respondents reported that the causes for kidney-related problems among returnee migrant workers were of unknown etiology and the most common risk factors for kidney-related problems (such as diabetes, hypertension) were usually absent. These indicate occupational renal risk of low-skilled Nepali migrant workers abroad. A similar pattern of the risk factors for kidney health was also observed among farmworkers in Central America.[23]

It has been speculated that a number of Nepali migrants return back to Nepal each year due to the kidney-related problems.[10,11]The Nepali Embassy in a key migrant destination country also acknowledges the rising cases of kidney-related problems among migrant workers.[18] Our findings also support this as nearly two-thirds of the respondents had ever treated migrant patients who were returned to Nepal only due to kidney-related problems. As patients show no symptoms, kidney-related problems are hard to diagnose in the early stages. Patients usually seek medical advice when the damage is already done and not possible to reverse.[24]

In April 2019, two of the authors (NA and PRR) carried out a patient public involvement event in Malaysia regarding kidney health-related issues of Nepali migrants.[18] Participating Nepali migrants shared some work-related circumstances which might precipitate risk to their kidney health. For example, migrant workers in the manufacturing sectors have a fixed schedule for going to the bathroom or having a drink because the manufacturing process can get disrupted in the absence of one worker.[18] There was also a concern of unavailability of potable water in many manufacturing sites in Malaysia, Nepali migrant workers frequently use a high dose of painkillers because they work continuously for several weeks without a day off, and security guards are allowed to use the toilet just twice a day due to the lack of replacement guards which force them to drink a little amount of water throughout the long work shift.[18]

CGN has been found to be one of the commonest causes of CKD in Nepal.[7] The earliest presentation of glomerulonephritis is asymptomatic hematuria and or hematuria, which can be easily detected by a routine urine test. If detected and treated early, most of the glomerulonephritis-associated CKD can be prevented. Although the general health check-up of the people going abroad as a migrant worker is mandatory in Nepal, at times the urinary findings, that could be clinically significant, might be overlooked. In the present study, glomerulonephritis has been reported as one of the key kidney health problems among returnee migrants. This warrants further improvements in the screening and early detection of this correctable renal entity not only before going abroad but also on a routine basis during their stay and working period in foreign countries.

Although there is limited evidence on kidney health-related risk among migrant workers, there is a preponderance of evidence in the last two decades regarding the markedly higher risk of CKD among farmworkers in Central America, Sri Lanka, Egypt, and in India.[23] This is often termed as "mesoamerican nephropathy"[25] or CKD with unknown aetiology.[23] The working conditions of these farmers and the majority of Asian migrant workers in GCC countries and Malaysia are largely similar, such as performing physically demanding work in a hot environment with recurrent dehydration.[19,26] There is evidence that the odds of AKI increased by 47% for each 5-degree Fahrenheit increment in the heat index,[26] and a heavy workload was associated with detrimental effects on kidney health,[27] and AKI was also observed among well-hydrated sugarcane workers in Guatemala.[28] These may contribute to kidney injuries individually or in combination.

There is some evidence that the simple intervention to prevent kidney damage could be effective, such as the implementation of water, rest, shade program in the United States of America positively influenced the biomarkers of kidney function.[24] Similar intervention could be carefully planned in the countries (e.g. Gulf, Malaysia) with a large number of labor migrants who often perform heavy physical work in heat stress.

This study assesses the need for large-scale studies on the kidney health risk of Nepali migrant workers. Although this was an online survey with nephrologists in Nepal, we were able to include more than three-quarters of its community.

Limitations of the study

This survey was limited by the non-participation of nephrologists currently working in the mid-western and far-Western part of the country. Seasonal migration to India is common in these regions, thus, the kidney health risk of Nepali cross border migrants in India is likely to be under-reported.

Also, the results might be prone to bias because this is dependent on nephrologists' recall of their migrant worker patients.

CONCLUSION

The present study shows that Nepali migrant workers, particularly males and those working in GCC countries and Malaysia, could be at higher risk of kidney health-related problems than the general Nepali population. CKD and glomerulonephritis were indicated as the most common kidney health-related problems in Nepali returnee migrants. Dehydration, heavy physical work, heat exposure, use of pain killers were suggested as potential risk factors. All respondent nephrologists believed that further scientific investigation is required to ascertain the magnitude of kidney health issues of Nepali migrants. Kidney function test is included in pre-departure health screening of Nepali labor migrants, however, the aspect of proper implementation is questionable. We highly recommend to the Department of Foreign Employment (Ministry of Labour) in Nepal to strictly monitor the implementation of pre-departure health screening. We also urge to include kidney health-related content in pre-departure orientation curriculum for aspiring migrant workers.

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NA, PRR- Conceived the study; **AS-** Co-ordinated for data collection in Nepal. All authors contributed to the questionnaire design; **NA-** Analysed the data and wrote the first draft of the manuscript; All authors helped with the revision of the manuscript and agreed on the final version

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Evaluation of a step-by-step approach to frozen section diagnosis in ovarian masses

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ABSTRACT

Background: Ovarian cancer forms a significant proportion of cancer-related mortality in females. It is often detected late due to non-specific clinical presentation. Radiology and tumor markers may indicate an ovarian mass. However, exact diagnosis requires pathological evaluation, which may not be possible before surgery. Intraoperative frozen section (FS) is, therefore, an important modality for the diagnosis of ovarian masses. **Aims and Objectives:** This study was conducted to study step-by-step approach along with diagnostic utility and accuracy of intraoperative FS in diagnosis of ovarian masses. **Materials and Methods:** Retrospective comparative analysis was done to determine the diagnostic accuracy of FS as compared to routine histopathology in the pathology department of a tertiary care hospital. Diagnostic categorization was done into benign, borderline, and malignant. Overall accuracy, sensitivity, and specificity of FS technique were calculated. **Results:** Out of 51 cases, FS analysis yielded accurate diagnosis in 94.1% of ovarian masses. Intraoperative FS had a sensitivity of 94.7%, specificity of 96.9%, 3.1% false-positive rate, and 5.3% false-negative rate in malignant tumors. In benign lesions, FS had 91.7% sensitivity and 100% specificity. FS had 75% sensitivity and 96.4% specificity in cases of borderline tumors. **Conclusion:** FS is a fairly accurate technique for intraoperative evaluation of ovarian masses. It can help in deciding the extent of surgery. It distinguishes benign and malignant tumors in most cases with high sensitivity and specificity. A methodical approach is useful in determining accurate diagnosis on FS diagnosis.

Key words: Accuracy; Frozen section; Ovarian tumors

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INTRODUCTION

Ovarian cancers account for 3.4% of all malignancies in women worldwide. It is one of the most lethal malignancies in females and presents a high burden of mortality.[1] Following breast and cervix, ovary is the third most common site for cancer in India, accounting for around 6% of all cancers in Indian women. It occurs more frequently in women aged between 45 and 65 years.[2] The patients may be asymptomatic or have non-specific symptoms such as abdominal fullness, bloating sensation, weight loss, and urinary frequency. Uncommonly, ovarian tumors may be accompanied by paraneoplastic syndromes such as recurrent venous thrombosis, seborrheic keratosis, or subacute cerebellar degeneration. Sex cord stromal tumors may manifest as hormone effects such as virilization.[3] Variable presentation and non-specific symptoms, may lead to late detection of ovarian cancer at an advanced stage, contributing to poor outcome.

Genetic and familial risk factors have been implicated in the development of ovarian cancers, and importance of careful clinical assessment including personal and family history cannot be emphasized more. Ultrasonography is usually the first line of investigation that may point toward the ovarian origin of mass and its cystic and/or solid nature. CA-125 is the most commonly used tumor marker in cases of suspected ovarian malignancy. However, it is neither very sensitive nor specific in distinguishing malignant ovarian tumors from benign lesions. Other tumor markers include serum alpha-fetoprotein, beta-human chorionic

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gonadotropin in germ cell tumors, and inhibin in sex cord stromal tumors.[3]

Further workup includes computerized tomography and/or magnetic resonance imaging.[4] In early stage ovarian cancer, surgery is potentially curative. Chemotherapy may be have to be added in advanced stage.[3] Intraoperative staging is done for malignant and borderline tumors with omentectomy, peritoneal washings, peritoneal biopsy, abdominal hysterectomy and bilateral salpingo-oophorectomy, and biopsy from retroperitoneal lymph nodes.[4] Frozen section (FS) can provide important information intraoperatively so that patients with benign ovarian lesions are spared from the morbidity associated with surgical staging.[5] Furthermore, fertility preservation may be valuable, particularly in younger patients, and extent of surgery can be decided with the help of FS.[5] At the same time, optimal staging may be performed once the diagnosis of borderline/malignant tumor is given on FS.[4] Subsequent histopathological examination (HPE) of the resected tissues is the diagnostic gold standard and guides the clinician in deciding further patient management.[4] FS has been used for head and neck, thyroid, and gynecological malignancies for intraoperative pathological assessment with reasonable accuracy.[6,7]

This study was conducted to study step-by-step approach and to determine the overall diagnostic accuracy and utility of intraoperative FS in ovarian masses, in a tertiary care hospital in Southwest Rajasthan.

Aims and objectives

This study aims to study step-by-step approach and to determine accuracy and diagnostic utility of intraoperative FS in ovarian masses.

MATERIALS AND METHODS

It was a retrospective study conducted in the Department of Pathology, Geetanjali Medical College and Hospital, Udaipur in Southern Rajasthan, India, after approval of the Institutional Ethical Committee. Cases of ovarian masses that were received for FS from May 2017 to April 2021, over a period of 4 years, were included in the study. HPE of formalin-fixed paraffin-embedded (FFPE) sections was taken as gold standard for diagnosis. Records of FS and FFPE reports were retrieved. Clinical information, demographic details, radiological findings, and tumor marker levels including CA-125 and cytology findings were included from previous records as and when available.

The specimens sent intraoperatively were sampled for FS. Gross specimen was examined in detail. Representative tissue bits were taken varying in number from 2 to 6 were taken, and frozen immediately using optimal cutting temperature compound – Leica Tissue Freezing Medium. Sectioning was done using Cryostat Leica CM 1860UV at 3–6 μm thickness. Hematoxylin and eosin (H and E) staining by the rapid method was performed and the sections were examined under microscope. The cell type (epithelial, stromal, germ cell, or sex cord), presence or absence of invasion, and growth pattern were studied in detail to determine the categories as benign, borderline, and malignant categories. After FS diagnosis was completed, the tissue samples for FS and rest of the specimen were fixed in 10% formalin and complete grossing was done the next day after fixation. These sections were processed in automatic tissue processor Leica TP 1020 as routine FFPE sections and stained with H and E staining using autostainer Thermo Scientific Gemini AS. Reporting was done as per routine protocol after FFPE sections were submitted after processing. Diagnosis on FFPE sections was considered as the gold standard with which diagnosis on FS was compared. Overall accuracy, sensitivity, specificity, false-positive rate, false-negative rate, positive predictive value, and negative predictive value were calculated. Concordant diagnostic categorization was considered true positive. In benign tumors, diagnosis of borderline or malignant tumor on FS was taken as false positive. In borderline tumors, diagnosis of benign tumor on FS was taken as false negative. In malignant tumors, benign or borderline categorization on FS was taken as false negative.[8]

RESULTS

A total of 51 cases were included in the study, with age ranging between 16 and 84 years. Mean age at presentation was 44.5 years. A large proportion of patients (47.1%) presented in the age ranging from 40 to 60 years followed by 21–40 years (37.3%). Few patients presented in <20 years and >60 years of age. Age distribution in benign, malignant, and borderline tumors showed wide variability (Table 1). Ascites was present in 12 out of 19 cases of malignant ovarian tumors and in 11 cases of benign lesions. The size ranged from 3.2–48 cm (Table 1).

On gross examination, the appearance of ovarian tumors varied from cystic uniloculated or multiloculated, solid cystic tumors, and solid tumors. Among malignant tumors, maximum cases (94.7%) had a solid component with or without cystic areas, whereas some tumors were largely cystic (5.3%). Solid cystic appearance of a malignant ovarian mass is shown in Figure 1. Borderline epithelial tumors on gross examination were solid-cystic (40%) and cystic (60%). Appearance of benign ovarian lesions showed varied gross appearance. Benign epithelial tumors were predominantly cystic. Fibromas and fibrothecomas had

a predominantly solid yellowish to whitish homogenous cut surface, while teratomas had a solid cystic cut surface. Size of the mass more than 10 cm did not show significant correlation with the presence of malignancy, as many of benign tumors were also large in size.

Neoplastic masses (78.4%) constituted the maximum number of cases (Table 2), while non-neoplastic lesions such as endometriosis, benign hemorrhagic cyst, and stromal edema were seen in 11 cases (21.6%). Eleven cases (27.5%) were bilateral and 29 (72.5%) were unilateral (72.5%). Histopathological features were studied in detail and categorization of tumors was done accordingly (Figure 2).

Epithelial tumors were the most common category (56.8%) including serous tumors (35.3%), mucinous tumors (13.7%), Brenner tumors (3.9%), and clear cell carcinoma (3.9%).

Table 1: Age and size of ovarian lesions at presentation

	Benign	Borderline	Malignant
Age (years)			
Range	18–71	16–54	23–84
Mean±SD	46.0±14.6	27.6±15.8	47.1±14.7
Size (cm)			
Range	3.2–25	16–48	4–27.5
Mean±SD	11.7±6.5	25.8±13.9	13.2±7.0

Table 2: Diagnostic categorization of ovarian masses

Category	N	%
Neoplastic		
Epithelial tumors		
Serous cystadenoma	5	9.8
Papillary serous cyst adenofibroma	1	2.0
Serous borderline tumor	3	5.9
Serous cystadenocarcinoma	9	17.6
Mucinous cystadenoma	3	5.9
Borderline mucinous tumor	2	3.9
Mucinous cystadenocarcinoma	2	3.9
Brenner tumor	2	3.9
Clear cell carcinoma	2	3.9
Germ cell tumors		
Teratoma	3	5.9
Sex cord stromal tumor		
Fibrothecoma	3	5.9
Granulosa cell tumor	3	5.9
Metastases		
Endometrial adenocarcinoma	1	2.0
Poorly differentiated carcinoma	1	2.0
Non-neoplastic		
Tuberculosis	1	2.0
Endometriosis	3	5.9
Hemorrhagic corpus luteum	1	2.0
Stromal edema and HGE	1	2.0
Stromal edema	1	2.0
Hemorrhagic cyst with torsion	1	2.0
Negative for malignancy	3	5.9
Total	51	100.0

Second most common group was sex cord stromal tumors (11.8%) followed by teratomas (5.9%) and metastases. Sub-categorization of ovarian masses is shown in Table 2.

Diagnoses of FS were compared with that of FFPE sections (Table 3). Out of 51 cases, on FS, 29 were diagnosed as benign lesions, three as borderline tumors, and 19 as malignant tumors. HPE of FFPE tissue sections revealed 27 benign lesions, five borderline tumors, and 19 malignant tumors. Out of 29 cases diagnosed benign on FS, 27 were benign on FFPE sections and two cases was underreported on FS. Out of 19 cases reported as malignant on FS, 18 were reported as malignant tumors on FFPE sections, while one was reported as borderline tumor. Out of five cases of borderline tumors on FFPE, three were diagnosed correctly on FS. One case was underreported as benign and one was overreported as malignant on FS.

Overall accuracy of FS for correct categorization of ovarian masses was 94.1%, with 94.7% sensitivity and 96.9% specificity in diagnosing malignant tumors, and 91.7% sensitivity and 100% specificity in diagnosing benign lesions (Table 4). For borderline tumors, FS had slightly lower sensitivity at 75%.

A methodical approach (Figure 3) by integrating the clinical and radiological details and other important investigations with the gross and histopathological features yielded accurate characterization in most cases.

DISCUSSION

Ovarian tumors can be classified into surface epithelial tumors, sex cord stromal tumors, and germ cell tumors.

Table 3: Diagnosis of benign, borderline, and malignant tumors on FS and FFPE sections

FS diagnosis	FFPE diagnosis			
	Benign	Borderline	Malignant	Total
Benign	27	1	1	29
Borderline	0	3	0	3
Malignant	0	1	18	19
Total	27	5	19	51

FS: Frozen section, FFPE: Formalin-fixed paraffin embedded

Table 4: Sensitivity, specificity, FPR, and FNR of frozen section in diagnosis of ovarian masses

	Benign	Borderline	Malignant
Sensitivity	91.7%	75%	94.7%
Specificity	100%	96.4%	96.9%
FPR	0	3.6%	3.1%
FNR	8.3%	25%	5.3%

FPR: False-positive rate, FNR: False-negative rate

Surface epithelial tumors are further categorized into benign, borderline, and malignant tumors. Germ cell tumors and sex cord stromal tumors can be benign or malignant. The distinction between benign, borderline, and malignant ovarian tumors is important to predict the prognosis as well as decide the management of the patient. Radiology can help in determining site and extent of tumor, but has limited value in exact characterization of ovarian neoplasms.[9]

Estimation of CA-125 is a part of routine workup of patients with suspected ovarian tumors. However, it has low specificity and sensitivity in differentiating benign lesions from malignant ovarian tumors.[10,11] CA-125 can be raised in non-neoplastic conditions such as adenomyosis and endometriosis, and in benign tumors such as leiomyoma of uterus.[11]

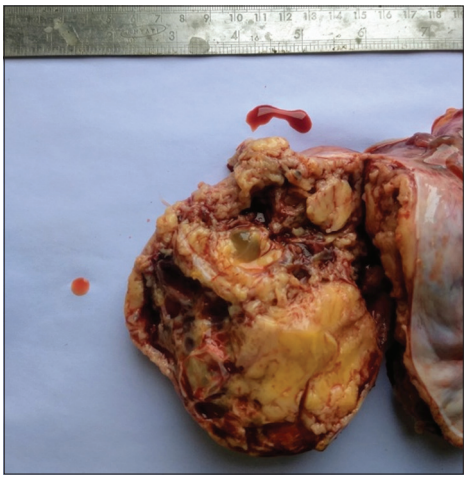

Figure 1: Gross appearance of malignant ovarian mass with solid cystic cut surface and areas of hemorrhage

Gross evaluation constitutes an important part of pathological examination of ovarian masses. Most of malignant tumors in our study showed a solid component with or without cystic areas, and few were cystic on gross appearance. Solid component can be detected in most of the malignant ovarian tumors.[12] and adequate sampling from solid areas or thickened areas may yield representative histopathology facilitating and accurate diagnosis on FS. Benign surface epithelial tumors are largely cystic, whereas stromal tumors such as fibrothecomas are solid with homogenous firm whitish to yellowish cut surface. Granulosa cell tumors are usually solid cystic. Germ cells tumors such as teratomas are usually cystic with or without solid areas, and the latter should be sampled to rule out immature component. Borderline tumors may are usually cystic, with or without solid areas, and thorough sampling needs to be done to rule out invasion. Presence of hemorrhage and necrosis may be seen in some of the malignant tumors. Sometimes, large ovarian tumors may undergo torsion with hemorrhagic infarction.

HPE of the resected tumor is the ultimate tool in diagnosis of ovarian tumors and additional investigations such as immunohistochemistry (IHC) may be required in some cases. However, FS can provide useful information intraoperatively for determining extent of surgery. FS technique is indicated intraoperatively for tumor diagnosis to decide the surgical management and evaluation of margins. It has been used widely in head-and-neck cancer. In cases where the site of origin is not clear in cytology, FS may be useful. It may be valuable for intraoperative confirmation of malignancy in cases where a pre-operative biopsy is unavailable.[6] FS is indicated where pre-operative diagnosis is not clear to determine the nature and malignant

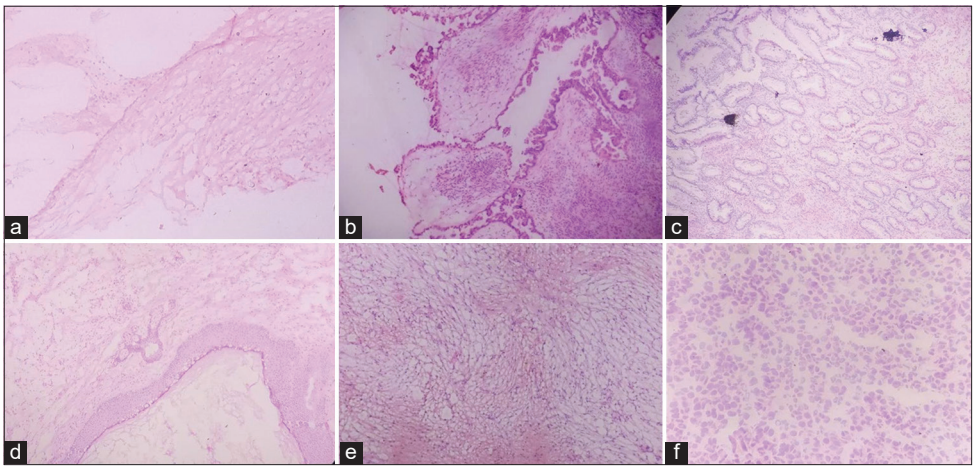

Figure 2: Histopathological features of ovarian tumors on FS; (a) serous cystadenoma: Cyst lined by flattened to cuboidal benign epithelium (H & E ×40); (b) serous borderline tumor: Lined by stratified epithelium with tufting and micropapillary architecture (H & E, ×10); (c) mucinous carcinoma: Neoplastic glands lined by mucinous epithelium with low-grade nuclear features (H & E, ×10); (d) teratoma: Stratified squamous epithelium and sebaceous glands (H & E, ×20); (e) fibrothecoma: Fascicular pattern with spindle cells and bland nuclei (H & E, ×10); (f) granulosa cell tumor: Uniform cells with bland appearing nuclei arranged diffusely and in cords (H & E, ×40)

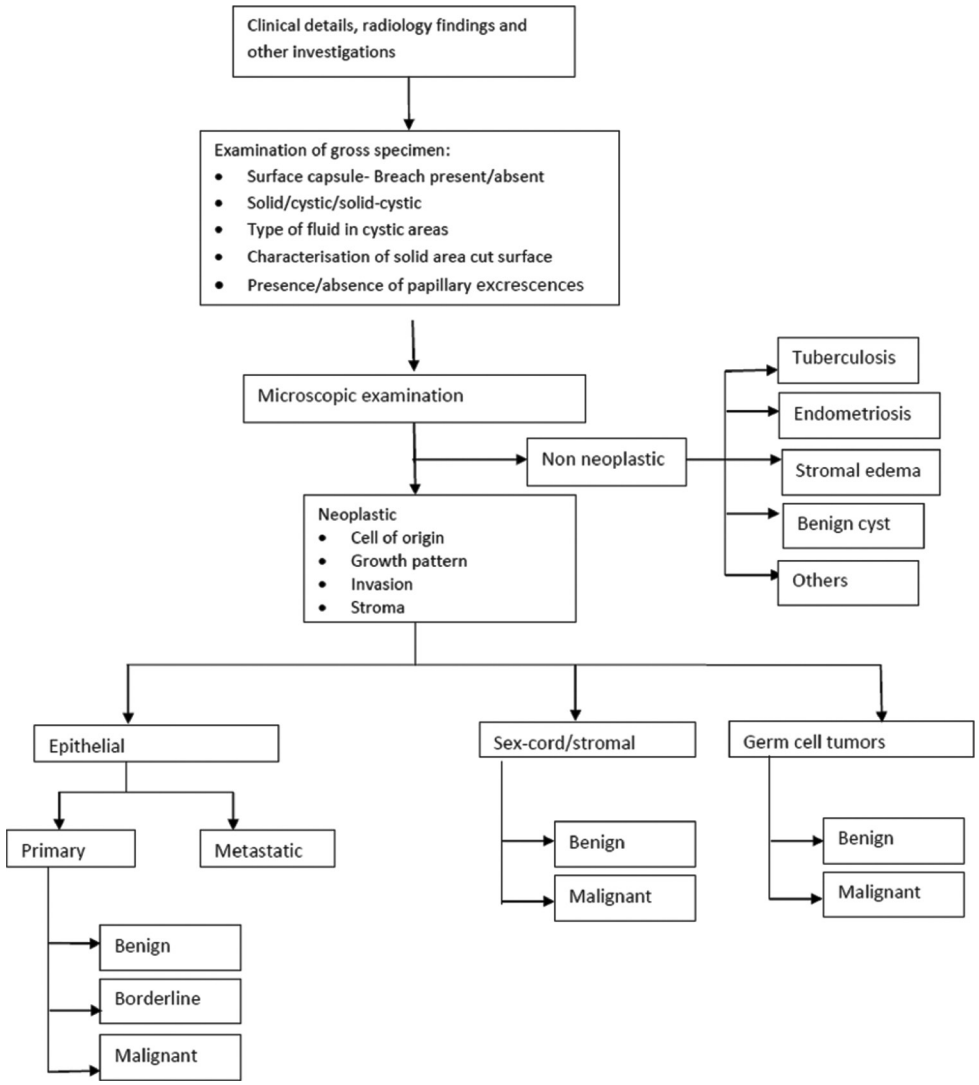

Figure 3: Step-by-step approach to frozen section diagnosis of ovarian masses

potential of ovarian masses.[8] FS has been found to be a reliable technique in gynecological neoplasms including endometrial and cervical cancer. In ovarian tumors, the diagnosis may not be established before surgery in many cases, and therefore, FS may provide important diagnostic information, which may guide the extent of surgery.[7]

FS allows microscopic examination of tissue in minimum time. In ovarian neoplasms, usually the excision specimen is sent for FS. Gross examination of tumor is available to the pathologist, and it can provide important clue to the diagnosis of ovarian masses. Frozen artifact may at times alter the morphology and make tissue interpretation difficult. In cases where large numbers of sections need to be sampled, final diagnosis may be made on the FFPE sections.

Incorporation of clinical data with available investigations, radiology findings, and operative findings can provide useful information. Proper gross evaluation with representative sampling by an experienced pathologist cannot be emphasized more. The microscopic examination should be done with the evaluation of architectural pattern, cytological features, and stromal characteristics. Methodical approach can guide the pathologist in interpretation of the histopathological features. First and foremost, categorization into neoplastic or non-neoplastic lesions needs to be done, followed by further subtyping. Non-neoplastic cases can be given appropriate diagnoses as per their morphological features. In neoplastic lesions, tumor architecture, pattern of growth, cellular and nuclear features, mitotic activity, presence or absence of invasion, and stromal characteristics should be examined in detail. Neoplasms can be subdivided as per their cell of origin, followed by further categorization into benign and malignant, as that is the most important piece of information a surgeon needs at an intraoperative stage to decide plan of immediate surgical management.

Borderline epithelial neoplasms may be difficult to accurately categorize on FS section in some cases. Such cases may be reported as at least borderline if invasion cannot be categorically commented on FS.[8] In some cases, particularly if suspicious areas are equivocal for malignancy, the diagnosis may have to be deferred for further sampling after fixation and routine tissue processing for a conclusive diagnosis.[5]

FS is a fairly sensitive and accurate technique for categorization of ovarian masses.[4] Various studies have reported the accuracy of FS in ovarian neoplasms ranging from 83% to 94.3% with high sensitivity and specificity.[5,12-15] During our study, accurate diagnostic categorization was possible in most cases (94.1%). For benign cases, FS was fairly sensitive (91.7%) and specific (100%). For malignant lesions, FS has a high sensitivity (94.7%) and specificity (96.9%) with low false-positive rate (3.1%) and false-negative rate (5.3%). These results are similar to the previous studies.[5,12-14] There were five cases of borderline ovarian tumors, out of which three were diagnosed correctly on FS. Borderline epithelial tumors can be difficult to diagnose on FS. Gross specimen is usually cystic with multiple loculations. As the nuclear atypia may be mild in benign and borderline tumors, multiple tissue sections may be required for definite diagnosis. Limited sampling in FS may pose a challenge in diagnosing such cases and definite categorization relies on FFPE sections. Underdiagnosis of malignancy may be a concern in borderline tumors, as mucinous tumors of the ovary are often heterogeneous, and further sampling may yield tissue sections with invasive component.[5,12] Large mucinous tumors with borderline component may be problematic.[13] Microscopic invasion may be difficult to assess on FS, due to artefactual aberrations. Any solid areas should be sampled and examined microscopically to rule out malignancy. The number of borderline tumors in our study was less and a larger study may help determine the exact accuracy of FS in cases of borderline epithelial tumors of the ovary.

In one case, differential diagnosis of primary ovarian versus metastatic carcinoma was kept. The ovaries were bilaterally enlarged with gray-white firm cut surface. Serum CA-125 and carcinoembryonic antigen levels were both raised. Final histopathology revealed a poorly differentiated adenocarcinoma. Careful gross and microscopic examination may indicate the origin of epithelial malignancy whether primary or metastatic. Bilateral involvement, multinodularity, surface involvement, and signet ring morphology of tumor cells are known to favor metastatic origin rather than primary ovarian carcinoma.[16] In some cases, the primary site of origin may not be ascertained radiologically, and IHC may be required for confirmation. IHC may help in distinguishing between primary ovarian carcinomas and adenocarcinomas of gastrointestinal origin.[17]

Teratomas are another group of tumors that may have different morphology in different areas. We came across a case of ovarian mass wherein the sections on frozen showed areas of mature teratoma with stratified squamous epithelium, skin adnexal structures, respiratory type epithelium, islands of mature cartilage, adipose tissue, and bone. However, on gross examination, the tumor was largely solid and a high suspicion for immature component was kept. After fixation, extensive sampling was done and subsequent FFPE sections revealed few areas with immature neuroepithelium indicating a Grade-I immature teratoma. The previous studies have reported discrepancies in FS results of teratoma, similar to our study. The area with immature component may not be sampled during FS and may be missed. Diagnosis in these cases requires adequate sampling, and final histopathological evaluation may be required for accuracy.[5]

Sometimes, the ovarian tumors can undergo necrosis or infarction that may be extensive and viable areas may be difficult to obtain on FS.[5] There may be hemorrhage and sometimes torsion in large masses, which may prevent accurate interpretation on FS, when extensive. Such cases may need more than adequate number of sections after fixation, to detect viable tumor areas, if present.

Apart from sampling error, other difficulties encountered by the pathologist during FS analysis includes frozen artifact. The tissue should be frozen immediately, as soon as it is received in the laboratory. Formation of ice crystals during frozen technique may result in suboptimal sections with morphological artifact and interpretation may be difficult.[5] Furthermore, time poses a constraint in FS diagnosis, particularly in cases that need extensive sampling.

In spite of multiple limitations and challenges, FS technique is a fairly sensitive tool to detect ovarian malignancy. Intraoperative FS gives the pathologist the opportunity for gross examination, and quick HPE of tissue, with determination of the nature of ovarian mass. The extent of surgery can thus be limited to an adequate excision, at the same time preventing overtreatment.

Limitations of the study

Further studies with a larger sample size would enhance the current understanding, particularly with regard to borderline tumors. Borderline epithelial tumors are one of the challenging areas in frozen section diagnosis. We encountered 5 cases of borderline tumors which is a small number. Also, inclusion of another pathologist for HPE reporting, blinded to the FS diagnosis could have removed the element of bias.

CONCLUSION

FS is a sensitive and specific technique for intraoperative evaluation of ovarian masses and accurate categorization is possible in most cases by following a step-by-step approach. Intraoperative FS allows correct categorization of ovarian masses in most cases and may provide important information to the surgeon, allowing him to take appropriate surgical decision. Borderline tumors and teratomas are a potential diagnostic pitfall in FS assessment of ovarian masses and final diagnosis may require FFPE sections in some cases.

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Role of magnetic resonance imaging in diagnosis and grading of perianal fistulas

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ABSTRACT

Background: Fistula-in-ano can be defined as a hollow tract or cavity which is lined by granulation tissue. In case of fistula-in-ano, one end of this fistula opens in the anal canal whereas the other end is located in perianal area. Fistula-in-ano can considerably affect quality of life of an individual because of perianal discharge of blood and pus. Imaging of these fistulas is an important part of management and MR imaging is important in assessing relationship between the fistulous tract and sphincter muscles. Moreover, MR imaging can reliably demonstrate transmural inflammation, secondary tracts/ramifications, and abscesses which cannot be diagnosed on the basis of conventional fistulography. **Aims and Objectives:** The aim of the study was to evaluate role of MRI in diagnosis and grading of perianal fistulae. **Materials and Methods:** This was a retrospective observational study, in which 60 patients with fistula-in-ano were included on the basis of a predefined inclusion and exclusion criteria. MR imaging of patients was done by 1.5 T MRI machine. Before MR imaging normal saline was injected in the fistulous tract from secondary/external opening, that is, opening around perianal area. Three plane images were obtained in all the cases. T1W, T2W, and STIR image sequences were obtained parallel to pelvic diaphragm. Coronal cuts were imaged parallel to anal canal. FAT suppressed T1W and T2W images in all cases. Type and grade of fistula were determined in all the cases. $P < 0.05$ was taken as statistically significant. **Results:** Out of total 60 patients, there were 46 (76.66%) males and 14 (23.33%) were females with a M:F ratio of 1:0.30. The mean age of male and female patients was found to be 41.93 ± 8.96 years and 44.04 ± 7.46 years, respectively. The most common type of fistula was found to be trans-sphincteric fistula which was seen in 31 (51.6%) cases followed by intersphencteric fistula 22 (36.6%). Extrasphincteric and suprasphincteric fistulae were relatively uncommon and were seen in 4 (6.66%) and 3 (5%) cases, respectively. MRI was accurate in diagnosis of the tract with position of internal opening and any abscess cavity or secondary tract in 23 patients. Therefore, the diagnostic accuracy of MRI was found to be 95.4%. **Conclusion:** MRI is an excellent tool in assessment of perianal fistula. It not only helps in precisely locating fistulous tract but also can demonstrate relationship between the fistulous tract and sphincter muscles. Moreover, it can very well demonstrate transmural inflammation, secondary tracts/ramifications, and abscesses which cannot be assessed by conventional fistulograms.

Key words: Magnetic resonance imaging; MR Fistulogram; Secondary tracts/ramifications; Sphincter muscles; Transmural inflammation

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INTRODUCTION

Fistula-in-ano can be defined as a hollow tract or cavity which is lined by granulation tissue. One end of this fistula opens in the anal canal whereas the other end is located in perianal area.[1] The opening in anal canal is called primary/internal opening whereas perianal opening is called secondary/external opening. There can be single or

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multiple secondary openings extending from same primary opening located in anal canal. These fistulae usually arise following perianal abscess. Fistula-in-ano has a tendency to chronicity and significantly affect quality of life.[2] The major problem associated with fistula in ano include discomfort resulting from continuous drainage from fistula leading to hygienic problems, in some cases this may cause serious complications such as septicemia.[3]

It is crucial to properly assess theses fistula-in-ano because surgical intervention must be aimed at not only eradication of fistulous tract thereby eradication of source of infection but also maintenance of continence which depends on maintenance of anal-sphincter complex.[4] Thus, pre-operative assessments of fistula-in-ano are one of the crucial components of management. Advanced imaging technique such as MR imaging has become crucial in identifying infected fistulous tracts and abscess that would have been impossible or at least difficult to assess by other conventional imaging methods.[5]

One of the common problems associated with conventional imaging methods such as conventional fistulograms is that while they can demonstrate the fistulous tract excellently, they usually fail to demonstrate the inflammatory process which has reached transmural tissue.[6] In this regard, MR imaging can be very helpful in knowing the involvement of tissue surrounding fistulous tract. Another limitation of conventional fistulogram is that it cannot demonstrate the relationship between the fistulous tract and sphincter muscles consequently involvement of internal and external anal sphincter as well as levator anti muscle cannot be ascertained, this limitation can be very well taken care of by MR fistulography.[7]

MR fistulography has the distinct advantage of not only depicting the fistulous tract but also it can demonstrate the extent of transmural inflammatory process secondary tracts/ramifications and abscesses. It also can precisely show the relationship between the fistulous tract and sphincter muscles.[8] Moreover, it can very well image a fistulous tract which is filled with pus and debris (Conventional fistulograms may fail to fill the tract if its blocked by debris).[9] Perianal fistulas are divided on the basis of relationship of the fistulous tract and the anal sphincter. The two most common classification system used are the Park's classification and the St James university hospital classification. The Park's classification is based on coronal imaging. The other classification and also the most accepted and convenient classification used is the St James university hospital classification.[10] In this classification, the presence of secondary tract or ramifications and perianal abscesses is also taken into consideration. Classification is based on both axial and coronal imaging. On the basis of Park's classification, the fistulas can be divided into intersphincteric, transsphincteric, suprasphincteric and extrasphincteric depending on the fistulous tract and its relationship with anal sphincters.[11]

We conducted this study to know role of magnetic resonance imaging in diagnosis and grading of perianal fistulas.

Aims and objectives

The aim of the study was to evaluate role of MRI in diagnosis and grading of perianal fistulae.

MATERIALS AND METHODS

This was a retrospective observational study, in which 60 patients with fistula-in-ano were included on the basis of a predefined inclusion and exclusion criteria. MR imaging of patients was done in the department of radiology of MGM Medical College and Hospital, Aurangabad using 1.5T MR imaging system.

Patients were explained in details about procedure of imaging as well as need for injection of normal saline in fistulous tract. An informed written consent was obtained from all the patients for injection of normal saline in fistulous tract and those who refused this injection out of fear of pain were excluded from this study. In all patients, it was ascertained that there was no contra-indication to MR imaging such as cardiac pacemakers, metallic implants, or aneurysmal clips. All patients were imaged in supine position. Before MR imaging normal saline was injected in the fistulous tract from secondary opening, that is, opening around perianal area. Three plane images were obtained in all the cases. T1W, T2W, and STIR image sequences were obtained parallel to pelvic diaphragm. Coronal cuts were imaged parallel to anal canal. FAT suppressed T1W and T2W images in all cases.

MR images were analyzed by senior radiologist for detection of internal as well as external opening, anatomical location and extent of fistulous tract, presence of scars, relationship of fistulous tract to sphincter muscles, and presence of transmural inflammation.

Fistula-in-ano was categorized on the basis of Park's classification.[11]

1. Intersphincteric - In it the fistulous tract lies in the intersphincteric space but does not traverse the external anal sphincter.
2. Transsphincteric - In this the fistulous tract traverses the external anal sphincter and then traverses through the ischioanal/ischiorectal fossa to open subcutaneously.

3. Suprasphincteric – Here, the fistulous tract traverses above in the intersphincteric space above the puborectalis muscle and then descends through the iliococcygeus muscle into the ischiorectal fossa
4. Extrasphincteric - Here the fistulous tact traverses through the ischiorectal fossa, the levator anti sphincter complex and opens into the rectum in the supra levator region, that is, above the anal sphincter.

Fistula-in-ano was graded on the basis of St Jame's University Hospital classification.[10]

Grade 1- It is the simplest type, that is, simple linear intersphincteric perianal fistulous tract.

Grade - Intersphincteric fistulous tract associated with secondary tract/ramification or abscess cavity.

Grade 3- Transsphincteric fistulous tact without any secondary tract or abscess.

Grade 4- Transsphincteric fistulous tract along with presence of secondary tract or ramification and/or abscess.

Grade 5- Any fistulous tract with supralevator or translavetor extension.

The statistical analysis was done using SSPS 21.0 software and $P<0.05$ was taken as statistically significant.

Inclusion criteria

The following criteria were included in the study:

1. Patients diagnosed to be having fistula-in-ano clinically or on the basis of conventional fistulograms.
2. Age of the patients above 18 years.
3. Those who gave consent to be part of study.

Exclusion criteria

The following criteria were excluded from the study:

1. Age <18 years.
2. Those who refused consent to be part of study.
3. Those who refused injection of normal saline in fistulous tract during imaging.
4. Patients having contraindication to MR imaging such as cardiac pacemakers, aneurysmal clips, or metallic implants not compatible with MR imaging.

RESULTS

A total of 60 patients diagnosed to be having perianal fistula wither clinically or on the basis of conventional fistulography were included in this study. Out of total 60 patients, there were 46 (76.66%) males and 14 (23.33%) were females with a M:F ratio of 1:0.30 (Figure 1).

The most common affected age group was found to be 41–50 years in males as well as female patients. Out of 60 studied cases 22 (36.67 %) males and 8 (13.33%) females belonged to age group of 41–50 years. The mean age of male and female patients was found to be 41.93±8.96 years and 44.04±7.46 years, respectively. The mean age of male and female patients was found to be comparable with no statistically significant difference (P=0.473) (Table 1).

The analysis of patients on the basis of presenting complaint showed that majority of the patients had a presenting complaint of perianal discharge which was seen in 35 (58.3%) patients followed by pain which was seen in 28 (46.67%) cases. 18 (30%) patients reported that their quality of life was significantly hampered due to perianal fistula (Table 2).

Among 60 cases in 49 (81.67%) patients, the cause of fistula in ano could not be established. Tubercular or bacterial infections were found to be the cause of fistula in 3 (5%) cases whereas recurrent abscess formation was found to be the cause of fistula in ano in 8 (13.33%) patients (Figure 2).

The fistulae were classified on the basis of Parks classification. The most common type of fistula was found to be transsphincteric fistula which was seen in 31 (51.6%) cases, followed by intersphincteric fistula (36.6%). Extrasphincteric and suprasphincteric fistulae were relatively uncommon and were seen in 4 (6.66%) and 3 (5%) cases, respectively (Table 3).

Grade 4 (Transsphincteric fistulous tract along with presence of secondary tract or ramification and/or abscess) fistula was found to be the most common type of fistula and was seen in 22 patients followed by Grade I (simple linear intersphincteric perianal fistulous tract) fistula which was seen in 20 (33.33%) patients. Grade 3 fistula (Transsphincteric fistulous tact without any secondary tract or abscess) was seen in 12 (20%) patients. Grade 2 and Grade 4 fistulae were less common and were seen in 4 (6.66%) and 2 (3.33%) cases, respectively (Figure 3).

The most sensitive sequence for detection of perianal fistula was found to be T2W images (96.6%), followed by T2FS images (STIR/SPAIR) (95%). The least sensitive sequence for detection of fistula was T1W images (86.6%). In this study, we found that the most common location for internal opening was posterior which was seen in approximately 70% of the patient, followed by anterior (11.65 %) and right lateral positions (10%). Out of the total 60 patients, perianal abscess or collection was found in 12 patients, that is, 20% of the patient (Figure 4). In 48 patients, no abscess cavity was localized. Secondary tract or ramifications were found in total 19 patients (31.4%) (Figure 5). No secondary tract or ramification was there

Table 1: Age distribution of the studied cases

Age group	Number of patients			
	Males		Females	
	Number of patients	Percentage	Number of patients	Percentage
18–30 years	2	3.33	0	0.00
31–40 years	14	23.33	3	5.00
41–50 years	22	36.67	8	13.33
51–60 years	5	8.33	2	3.33
>60 years	3	5.00	1	1.67
Total	46	76.66	14	23.33
Mean Age	41.93±8.96		44.04±7.46	

P=0.4273 (Not significant)

Table 2: Presenting complaints of the studied cases

Complaint	Number of patent	Percentage
Perianal discharge	35	58.33
Pain	28	46.67
Significantly affected quality of life	18	30.00
Recurrent abscess formation	5	8.33

Table 3: Classification of fistula on the basis of Parks classification

Types	Number of patient	Percentage
Intersphincteric	22	36.6
Transsphincteric	31	51.6
Suprasphincteric	3	5
Extrasphincteric	4	6.66

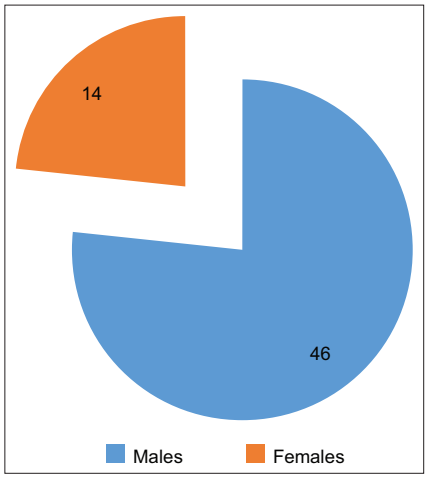

Figure 1: Gender distribution of the studied cases

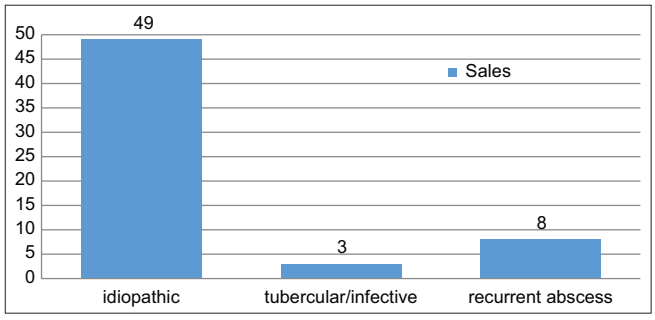

Figure 2: Etiology of perianal fistula in studied cases

in 41 patients (68.6%). 24 patients underwent surgery in our institute. MRI was accurate in diagnosis of the tract with position of internal opening and any abscess cavity or secondary tract in 23 patients. Therefore, the diagnostic accuracy of MRI was found to be 95.4%.

DISCUSSION

A total of 60 patients having perianal fistula were included in this study. Out of total 60 patients, there were 46 (76.66 %) males and 14 (23.33 %) were females with a M: F ratio of 1:0.30. Abbas et al. conducted a study of patients with anal fistula secondary to cryptoglandular disease and to determine factors that influence post-operative outcome.[12] In this an overwhelming majority of patients were males (79.3%). Similar male preponderance was also reported by the authors such as Stewart et al.[13] and de Miguel Criado et al.[14]

In our study, mean age of male and female patients was found to be 41.93±8.96 years and 44.04±7.46 years, respectively. The mean age of male and female patients was found to be comparable with no statistically significant difference (P=0.473). Sainio conducted a study of 458 patients to determine incidence and epidemiology of anal fistula during a 10-year period. The authors found that at the time of diagnosis the mean age of the patients was 38.3 years. The mean age of affected cases in this study was similar to our study.[15]

In our study, perianal discharge (58.3%) followed by pain (46.67%) was common presenting complaints. In 49 (81.67%) patients, the cause of fistula in ano could not be established. Tubercular or bacterial infections were found to be the cause of fistula in 3 (5%) cases

Table 4: Characteristics of fistula-in-ano on MR imaging and diagnostic accuracy of MRI

Characterstic	Sequence	Number of patient	Percentage
Diagnostic Accuracy of Various MRI Sequences	TIW images	52	86.6
	T2W images	57	95
	T2FS/STIR	56	93.3
Location of Internal Opening	Anterior	7	11.67
	Posterior	42	70.00
	Right Lateral	6	10.00
	Left Lateral	5	8.33
Presence of Abscess/Collection	Present	12	20
	Not present	48	80
Secondary Tract or Ramifications	Present	19	31.6
	Absent	41	68.4
Diagnostic Accuracy of MRI	Accurate	23	95.8
	Not accurate	1	4.2

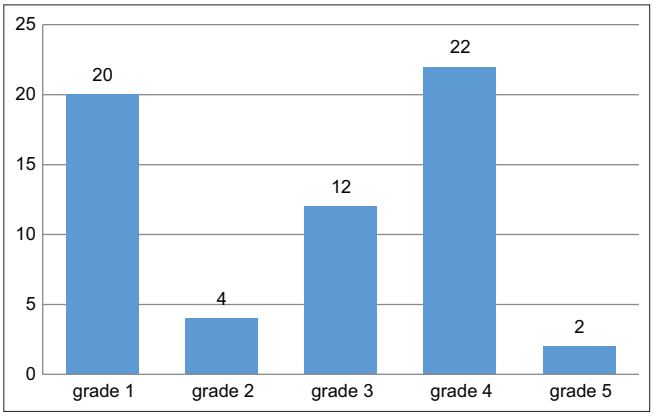

Figure 3: Grading of fistula in studied cases

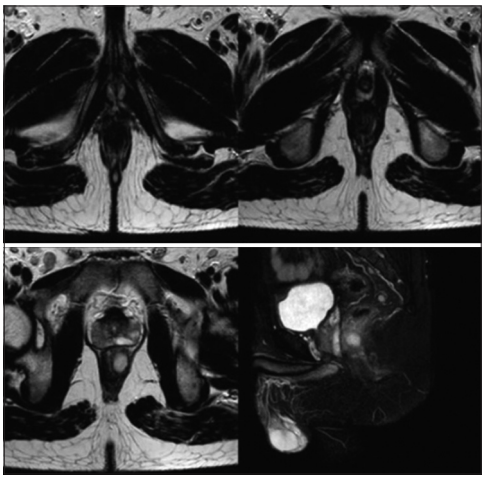

Figure 4: A transsphincteric fistulous tract was seen giving a branching in intersphincteric region with intersphincteric abscess formation

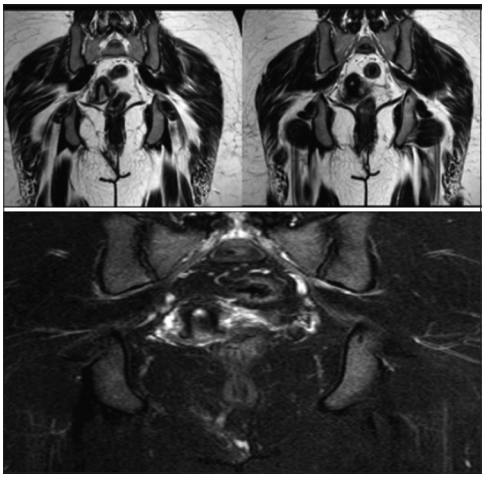

Figure 5: MR fistulography showing a transsphincteric fistulous tract traversing through the right ischioanal region, piercing the external anal sphincter with internal opening into anal canal

whereas recurrent abscess formation was found to be the cause of fistula in ano in 8 (13.33%) patients. The most common type of fistula was found to be transsphincteric fistula which was seen in 31 (51.6%) cases followed by intersphincteric fistula (36.6%). Extrasphincteric and suprasphincteric fistulae were relatively uncommon and were seen in 4 (6.66%) and 3 (5%) cases, respectively. Most of the studies have reported idiopathic type to be the commonest etiological type of perianal fistula.[16]

In our study, Grade 4 fistula was found to be the most common type of fistula and was seen in 22 patients, followed by Grade I fistula which was seen in 20 (33.33%) patients. Grade 3 fistula was seen in 12 (20%) patients. Grade 2 and Grade 4 fistulae were less common and were seen in 4 (6.66%) and 2 (3.33%) cases, respectively. In a similar study Chaudhari et al. studied MRI images of 35 patients with different types of perianal fistulas. Imaging was performed with multiplanar T1-weighted, T2-weighted, and PDFS sequences. The authors found that out of 35 studied cases 18 (51%) patients showed Grade 1 (simple linear intersphincteric fistula), 5 (14%) showed Grade 2 (intersphincteric with abscess or secondary tract), 6 (21%) showed Grade 3 (transsphincteric), 5 showed Grade 5 (14%) (transsphincteric with abscess

or secondary tract in ischiorectal or ischioanal fossa), and none (0%) showed Grade 5 (supralevator and translevator).[17]

In our study, the most sensitive sequence for detection of perianal fistula was found to be T2W images (96.6%), followed by T2FS images (STIR/SPAIR) (95%). The least sensitive sequence for detection of fistula was T1W images (86.6%). In a similar study conducted by Madireddy et al., the authors found that MR fistulography was 97.29% sensitivity, 66.66% specific and had 94% positive predictive value, 50% negative predictive value, and overall diagnostic accuracy of 95% in the diagnosis of perianal fistula.[18] These findings were similar to the findings of our study which found overall diagnostic accuracy of MR imaging for diagnosis of perianal fistula to be 95.8%. Similar diagnostic accuracy was also reported by the authors such as Daabis et al.[19] and Singh et al.[20]

Limitations of the study

The limitations of this study included the problem with alignment of MRI images with anal canal axis. Another limitation of study was limited number of patients. Larger studies are required to further substantiate the outcome of this study.

CONCLUSION

MR imaging of perianal fistula is an excellent tool in assessment of perianal fistula. It is not only useful in diagnosis of fistulae but also can precisely demonstrate the presence of transmural inflammation, secondary tracts/ramifications, and abscesses. It also helps in precisely locating fistulous tract but also can demonstrate relationship between the fistulous tract and sphincter muscles consequently involvement of internal and external anal sphincter as well as levator anti muscle can be reliably ascertained.

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SSK, DBD- Concept and design of the study; interpreted the results, prepared first draft of manuscript and critical revision of the manuscript; **SGP-** Statistically analyzed and interpreted; reviewed the literature and manuscript preparation; **VD-** Design of the study, statistically analyzed and interpreted, preparation of manuscript and revision of the manuscript; **SP, TAP-** Concept and coordination of the overall study.

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ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

A comparative study of propofol based total intravenous anesthesia and sevoflurane based volatile induction and maintenance anesthesia on post-operative recovery profile in elective tonsillectomy

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ABSTRACT

Background: Tonsillectomies are common surgeries in day-to-day surgery practice particularly in pediatric age group. Recent trend is to conduct tonsillectomy surgery on a day care basis. It is important to use the best anesthetic option with the least recovery time to reduce the hospital stay of patient. **Aims and Objectives:** The aim of the study was to compare recovery profile and side effects of Sevoflurane and Propofol as an anesthetic agent for tonsillectomy. **Materials and Methods:** A total of 60 patients undergoing elective tonsillectomy were selected for the study. Each patient was randomly allocated to either the propofol (Group P) or the sevoflurane group (Group S). Time of surgery (From start to end of surgery), time of anesthesia (From the start of induction to end of surgery), time between the end of anesthesia and the spontaneous eye opening, and time between the end of anesthesia and the following of verbal commands. Time to extubation, time between the end of anesthesia, and the orientation to his or her name and the incidence of post-operative nausea and vomiting were compared in both the groups. **Results:** The eye opening in Group P patients was found to be 8.9 + 1.21 min and that in Group S was 6.6 + 1.25 which was found to be statistically significant. The following of verbal commands in Group P was found to occur at 10.13 + 1.28 min, while that in Group S was found to be at 7.63 + 1.25 min, which was statistically significant. The time for extubation in Group P was found to be 11.17 + 1.29 min, while that in Group S was found to be 8.67 + 1.24 min, which was statistically significant. The duration for complete orientation in Group P was found to be 12.2 + 1.27 min, while that in Group S was found to be 9.43 + 1.04 min, which came out to be statistically significant. Hemodynamic parameters were found to be comparable in both the groups with no statistically significant difference in between then at any point of time ($P > 0.05$). **Conclusion:** Sevoflurane is a useful alternative to propofol in providing anesthesia where rapid emergence and recovery of cognitive functions are desired.

Key words: Day care surgeries; Propofol; Recovery; Sevoflurane; Tonsillectomy

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INTRODUCTION

Tonsillitis is a common occurrence particularly in pediatric age group. Tonsillectomy with or without adenoidectomy is a long practiced and one of the most frequently performed surgical procedures in pediatric age group worldwide.[1] The number has declined by approximately 50% from about 1.4 million in 1959 to about 2 lakh per

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year till date. Although a commonly performed procedure, it poses a great challenge to the surgeon as well as the anaesthesiologist and is associated with a substantially increased risk of morbidity and mortality.[2]

The rise in incidence of tonsillectomy is one of the major phenomenon, around 200,000 tonsillectomies are done annually in India. Obstructive sleep apnea is marked by interruptions in breathing while asleep and is common among children with enlarged tonsils or adenoids.[3] The absolute indications of the procedure are enlarged tonsils with features of upper airway obstruction, dysphagia, sleep disorders, peritonsillar abscess not adequately responding to medical management, febrile seizures due to tonsillitis, and tonsillar pathology requiring biopsy for a definitive diagnosis.[4]

Recent trend is to conduct tonsillectomy surgery on a day care basis. It is important to use the best anesthetic option with the least recovery time to reduce the hospital stay of patient. Ambulatory anesthesia is one administered for elective surgical procedure performed on carefully selected patients, which is undertaken with all its constituent elements (admission, surgery, and discharge home) on the same day. It is also referred to as day case, day care or outpatient anesthesia and more recently office-based anaesthesia.[5] Ambulatory anesthesia is a rapidly growing subspecialty. Although its history is as old as the history of general anesthesia itself, it has emerged as a recognized concept and is evolving over the past couple of decades. Anesthetic agents today have been designed and marketed to meet specific niche criteria for ambulatory anesthesia. Among the agents available in India, propofol and sevoflurane have increased the ability of the anaesthesiologist to provide a successful day care experience. A common strategy used in routine clinical practice is to perform the induction with an intravenous formulation (such as propofol) and to continue maintenance with an inhaled agent (such as sevoflurane). While numerous studies have been published comparing inhaled versus intravenous agents for the induction and maintenance of anesthesia in several surgical procedures, study protocols vary with regard to pre-medication, inhalational agents, fresh gas flow rates, additional opioids usage, and the type and duration of surgery.[6]

Sevoflurane and propofol are the agents that can be used for day care surgeries with minimal side effects and early recovery.[7] Sevoflurane has many features of an ideal inhalational agent; its low blood-gas solubility and non-pungent smell suggest a smooth, uncomplicated and rapid induction of, and emergence from, anesthesia. Sevoflurane is an attractive option for "volatile Induction maintenance anesthesia" which is proposed to prevent the problems associated with the transition phase between intravenous induction and inhalational maintenance. These properties may make sevoflurane especially suitable for day surgery. The pharmacokinetics of propofol allows rapid induction of anesthesia, adequate maintenance, and rapid recovery of consciousness and reduces post-operative morbidity such as nausea, vomiting, and respiratory depression. These two general anesthesia procedures are used in oral and maxillofacial surgeries for the realization of patient comfort and/or invasive surgery application.[8]

During the recovery period, vital finding changes encountered in the follow-up, post-operative pain and post-operative nausea vomiting are among the post-operative complications frequently encountered. Post-operative complication frequency in the patients, their recovery periods and their states to be able to go to their service departments could display differences depending on surgery and anesthesia procedures.[9]

The present study will help in making a choice between these two agents on the basis of their recovery profile and side effects to facilitate tonsillectomy as a day care surgery.

Aims and objectives

The aim of the study was to compare recovery profile and side effects of Sevoflurane and Propofol as an anesthetic agent for tonsillectomy.

MATERIALS AND METHODS

The study was prospective randomized comparative single center study conducted in the department of anesthesiology of Dr Shankarrao Chavan Government Medical College and Hospital Vishnupuri Vanded. Institutional ethical committee approved the study (vide letter no SCGMC/217/03/17). The period of study was from January 1, 2018, to June 30, 2020. A total of 60 patients undergoing elective tonsillectomy were selected for the study. All the patients were assessed and those with normal clinical, biochemical, radiological, and hematological parameters were selected. Informed written consent was obtained from all the patients and parents in case of minor.

A total of 60 patients were selected for the study. Each patient was randomly allocated to either the propofol or the sevoflurane group. Randomization was done using a computer-based table of random numbers. The groups were named:

Group P - Consisted of 30 patients in whom induction and maintenance was done with intravenous anesthetic agent propofol.

Group S - Consisted of 30 patients in whom induction and maintenance was done with inhalational anesthetic agent sevoflurane.

A thorough pre anesthetic evaluation was done including history and general examination. All patients were kept nil per oral before surgery according to standard protocol. Procedure was explained to the patient and informed consent was obtained. After shifting the patient to Operation theater an intravenous drug line was secured with 20 G venous cannula in the non-dominant arm and an infusion of ringer lactate solution was started. Intraoperative monitoring devices such as electrocardiography, pulse oximetry, non-invasive blood pressure, and end-tidal carbon dioxide monitor were attached to patient. All the patients were premedicated with Inj. Glycopyrrolate 0.01 mg/kg I.V, Inj. Midazolam 0.05 mg/kg IV. The patients were not given any IM premedication. Since many large randomized controlled trials have concluded that there is no rationale for the prophylactic administration of antiemetic drugs in oral and maxillofacial surgical procedures so prophylactic antiemetic were not given. They were assessed with particular attention to any contraindications. The tests for recovery and the importance of strictly following instructions were emphasized.

Conduct of anesthesia

Group P (PROPOFOL GROUP): 30 patients. These patients were induced with bolus injection of propofol 3 mg/kg IV and intubated with 0.5mg/kg atracurium. After confirming and securing the endotracheal tube in position, they were connected to the closed circuit with nitrous oxide and oxygen in 60:40 ratio to maintain normocapnia. Immediate post-intubation, this group of patients received a continuous infusion of propofol 100–250 mcg/kg/min to maintain an adequate depth of anesthesia as judged by clinical signs and hemodynamic responses to surgical stimuli.

Group S (SEVOFLURANE GROUP): 30 patients. These patients were induced with sevoflurane 7% by patient-controlled inhalation induction, that is, spontaneous ventilation and intubated with 0.5 mg/kg atracurium. After confirming and securing the endotracheal tube in position, they were connected to the closed circuit with nitrous oxide and oxygen in 60:40 ratio to maintain normocapnia with sevoflurane 2–3% to maintain adequate depth of anesthesia.

Throughout the procedure, heart rate, SPO_2, and blood pressure were monitored and recorded at regular intervals and ECG was monitored continuously. All patients were given appropriate maintenance fluid in form of IV Ringer lactate and were continued in the post-operative period until they start taking oral fluids. For pain management, Inj. Paracetamol 15 mg/kg IV was given to each patient after induction of anesthesia. Once the surgery was over, neuromuscular blockade was antagonized with Inj. neostigmine 40 mcg/kg and Inj. glycopyrrolate 10 mcg/kg. The trachea was extubated when the gag reflex had returned and the patient started breathing spontaneously and showing purposeful movement of all extremities and opened the eyes. Then, the patient was placed in the lateral decubitus position. The time of discontinuing the agent was taken as "time zero" to calculate the recovery time. After extubation, patients were transferred to the recovery room. In the recovery unit, all patients were oxygenated by facemask. Heart rate, non-invasive blood pressure, and respiratory rate were recorded.

All patients were monitored continuously for

1. heart rate and respiratory rate – before induction, at induction, at incision, and throughout intraoperative period.
2. Systolic and diastolic blood pressure levels, mean arterial pressure – before induction, at induction, at incision and throughout intraoperative period.
3. SPO_2 – Before induction, at induction, at incision, and throughout intraoperative period Following observations were obtained:

Time of surgery (From start to end of surgery), time of anesthesia (From the start of induction to end of surgery), time between the end of anesthesia and the spontaneous eye opening, and time between the end of anesthesia and the following of verbal commands. Time to extubation from the end of anesthesia to extubation, time between the end of anesthesia, and the orientation to his or her name and the incidence of post-operative nausea and vomiting were compared in both the groups. Patient was followed up postoperatively for 24 h.

Sample size was calculated according to the previous reference studies where propofol based total intravenous anesthesia and sevoflurane based volatile induction and maintenance anesthesia was compared. At least 30 patients in each arm were required as calculated by Open Epi-Version 3 online software, a 10% difference could be determined between the group at 80% power and 5% significance (α=0.05, β=0.80). The data were analyzed using Statistical Package for the Social Sciences version 21.0 for windows. Student "t" test was used to test for statistical significance in the differences of the two means. $P<0.05$ was taken as statistically significant.

Inclusion criteria

The following criteria were included in the study:

- Assessed patients of ASA physical status I and II undergoing tonsillectomy.
- Normal biochemical and hematological parameters.
- Age group between 05 and 25 years.
- No known hypersensitivity to egg or drug.
- Airway – MPC I and II

Exclusion criteria

The following criteria were excluded from the study:

1. Those who refused consent.
2. ASA class III and above.
3. Patients with H/O drug or egg allergy.
4. Anticipated difficult airway.
5. H/O serious adverse experience with anesthesia.
6. Severe CVS/RS/CNS/Metabolic disease

RESULTS

A total of 60 patients of ASA I and II between the age group of 05–25 years of either sex posted for elective tonsillectomy were selected for the study. They were randomly divided into two groups. Group P and Group S in which Group P denotes patients who received induction and maintenance with propofol and Group S denotes patients who received induction and maintenance with sevoflurane.

In our study, 56.6% of Group P and 66.67% of Group S patients were in the age group of 5–9 years. In 10–14years age group, 36.67% were in Group P and 20% in Group S. About 6.67% of Group P and 13.33% of Group S were in the age group of 15–19 years. No patients were in the age group of 20–25 years. There was no significant difference in age distribution between the two groups (P>0.05). In Group P, 19 patients were male and 11 patients were female. In Group S, 16 patients were male and 14 patients were female. There was no any significant difference in gender distribution between the two groups (P=0.432). The mean weight in Group P was 21.1±5.24 kg while in Group S was 20.47±5.50 kg, there was no significant difference in body weight distribution between the groups (P>0.05). In Group P and Group S, 26 patients were under ASA I grade and four patients were under ASA II grade. There was no statistically significant difference between ASA score among the study groups (P=1). In our study, duration of surgery in Group P was 41.46+3.18 min and in Group S it was 43.03+3.58 min. This was found to be statistically not significant (P>0.05). Further the duration of anesthesia in Group P was 56.5+3.81 min and in Group S it was 57.2+3.04 min which was found to be statistically not significant (P>0.05) (Table 1).

In our study, the eye opening in Group P patients was found to be 8.9+1.21 min and that in Group S was 6.6+1.25 which was found to be statistically significant.

The following of verbal commands in Group P was found to occur at 10.13+1.28 min., while that in Group S was found to be at 7.63+1.25 min, which was statistically significant.

Table 1: Age, gender, weight, ASA grades, duration of surgery, and duration of anesthesia in both the groups

	Group P n (%)	Group S n (%)
Age (years)		
5–9	17 (56.67%)	20 (66.67%)
10–14	11 (36.67%)	6 (20%)
15–19	2 (6.67%)	4 (13.33%)
20–25	0	0
Mean±SD	9.43+2.7	9.53+2.8
Unpaired t test and P value	t=0.1408, d.f=58, P=0.89	
Gender distribution		
Male	19 (63.33%)	16 (53.33%)
Female	11 (36.67%)	14 (46.67%)
Unpaired t test and P value	t=0.617, d.f=1, P=0.432	
Weight (kg)		
11–15	2 (6.67%)	8 (26.67%)
16–25	21 (70%)	16 (53.33%)
26–35	7 (23.33%)	6 (20%)
Mean±SD	21.1+5.24	20.47+5.50
Unpaired t test and P value	t=0.45, d.f=58, P=0.65	
ASA grades		
I	26 (86.67%)	26 (86.67%)
II	4 (13.33%)	4 (13.33%)
Duration of Surgery (From start to end of surgery)	41.46+3.18	43.03+3.58
	t=1.79, d.f=58, P=0.07	
Duration of Anesthesia anesthesia (From the start of induction to end of surgery)	56.5+3.81	57.2+3.04
	t=0.79, d.f=58, P=0.43	

The time for extubation in Group P was found to be 11.17+1.29 min, while that in Group S was found to be 8.67 +1.24 min, which was statistically significant.

The duration for complete orientation in Group P was found to be 12.2+1.27 min, while that in Group S was found to be 9.43+1.04 min, which came out to be statistically significant (Table 2). Patients in sevoflurane group thus were found to have a faster recovery profile as compared to patients in Propofol group.

The analysis of parameters such as heart rate parameters, respiratory rate, systolic and diastolic blood pressures, mean arterial pressures, respiratory rate, and SPO_2 showed that these parameters were comparable in both the groups throughout the time period extending from pre-induction up to 60 min of induction. These parameters were compared in both the groups at an interval of 5, 10, 15, 30, 45, and 60 min. All these parameters were found to be comparable in both the groups with no statistically significant difference in between then at any point of time (P>0.05) (Table 3) and (Figures 1-6).

The incidence of post-operative nausea vomiting was higher in Group S (16.67%) than Group P (3.33%); however, this difference was not found to be statistically significant (Table 4).

Table 2: Comparison of time taken to eye opening, verbal commands, extubation, and orientation

Parameter Duration (minutes)	Group P Mean ± SD (In minutes)	Group S Mean ± SD (In minutes)	Unpaired t test and P value
Eye opening	8.9+1.21	6.6+1.25	t=7.24, d.f=58, P<0.01
Verbal command	10.13+1.28	7.63+1.25	t=7.65, d.f=58, P<0.01
Extubation	11.17+1.29	8.67+1.24	t=7.65, d.f=58, P<0.01
Orientation	12.2+1.27	9.43+1.04	t=9.24, d.f=58, P<0.01

DISCUSSION

Rapid emergence from anesthesia and post op recovery of cognitive function as well as hemodynamic stability is important requirements of modern anesthesia. Propofol is a short-acting general anesthetic agent used widely for total intravenous anesthesia because of its favorable recovery profile and low incidence of side effects. Propofol infusions are also becoming increasingly popular for maintenance of anesthesia. However, the use of propofol is associated with pain on injection, cardiovascular, and respiratory depression and requires an intravenous drug delivery system.[10]

Sevoflurane is a safe and versatile inhalational anesthetic compared with currently available agents. Sevoflurane is useful in adults and children for both induction and maintenance of anesthesia in inpatient and outpatient surgery. Of all currently used anesthetics, the physical, pharmacodynamics, and pharmacokinetic properties of sevoflurane come closest to that of the ideal anesthetic. These characteristics include inherent stability, low flammability, non-pungent odor, lack of irritation to airway, and low blood: Gas solubility allowing rapid induction of and emergence from anesthesia, minimal end-organ effects, minimal effect on cerebral blood flow, low reactivity with other drugs, and a vapor pressure and boiling point that enables delivery using standard vaporization techniques. The aim of this study was to compare the propofol based total intravenous anesthesia and sevoflurane based volatile induction and maintenance anesthesia on post-operative recovery profile in elective tonsillectomy.[11]

In our study, in Group P and Group S, 26 patients were under ASA I grade and four patients were under ASA II grade. There was no statistically significant difference between ASA score among the study groups (P=1). No statistically significant difference was determined between the groups in respect of patient characteristics and ASA scores. Findings of authors such as Fredman et al. were

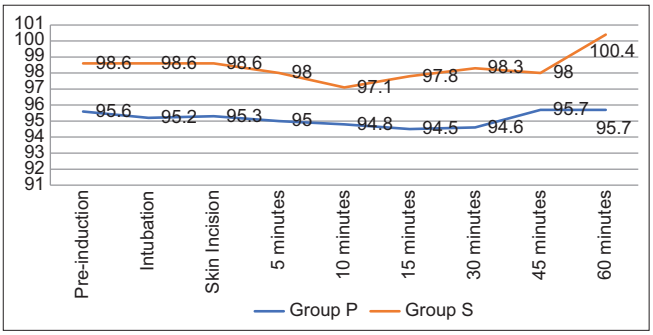

Figure 1: Comparison of mean heart rate in both the groups

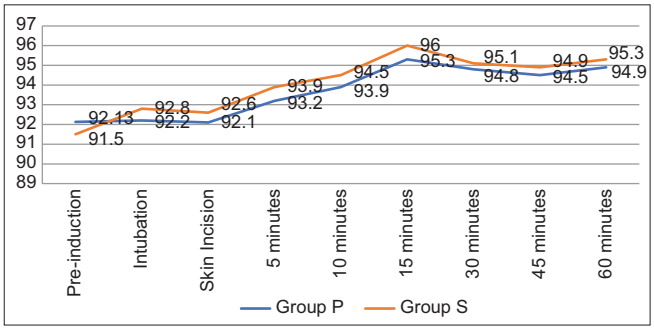

Figure 2: Comparison of mean systolic blood pressure in both the groups

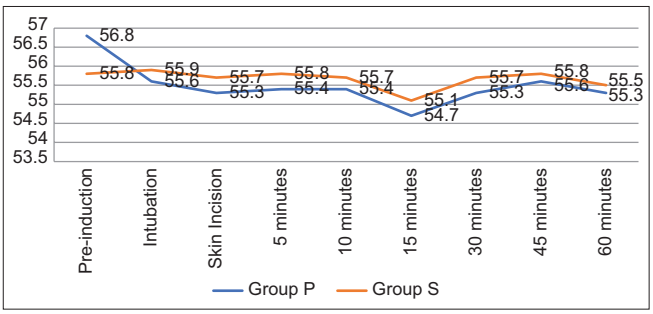

Figure 3: Comparison of mean diastolic blood pressure in both the groups

found to be comparable with our study. They also found no statistical difference in respect to patient characteristics and ASA scores.[12]

In our study, time taken for eye opening from termination of anesthetic was significantly shorter with sevoflurane group when compared with propofol group (P<0.01). In sevoflurane group, it was 6.6+1.25 min whereas it was 8.9+1.21 min in propofol group. Choi et al. found that spontaneous eye opening in sevoflurane group was shorter than propofol group which is similar as our study.[13]

However, Shah and Adaroja study concluded that compared to propofol group (5.41±0.99 min), the emergence times from cessation of the administration of the anesthetic agent to spontaneous eye opening was significantly

Table 3: Comparison of hemodynamic parameters in both the cases

	Group P Mean± SD (n=30)	Group S Mean±SD (n=30)	Unpaired t test and p value
Heart rate			
Pre-induction	95.6+8.7	98.6+7.7	t = 1.41, d.f = 58, P = 0.16
Intubation	95.2+8.1	98.6+7.8	t = 1.65, d.f = 58, P = 0.10
Skin incision	95.3+8.2	98.6+7.4	t = 1.66, d.f = 58, P = 0.10
5 min	95+7.68	98+7.6	t = 1.52, d.f = 58, P = 0.13
10 min	94.8+7.2	97.1+6.4	t = 1.3, d.f = 58, P = 0.19
15 min	94.5+8.2	97.8+8.2	t = 1.56, d.f = 58, P = 0.12
30 min	94.6+7.8	98.3+8.3	t = 1.78, d.f = 58, P = 0.08
45 min	95.7+7.5	98+7.4	t = 1.20, d.f = 58, P = 0.24
60 min	95.7+7.8	100.4+6.9	t = 2.47, d.f = 58, P = 0.01
Systolic blood pressures			
Pre-induction	92.13±8.2	91.5±7.4	t = 0.31 d.f = 58, P = 0.75
Intubation	92.2±7.3	92.8±7.1	t = 0.32 d.f = 58, P = 0.74
Skin incision	92.1±7.5	92.6±6.9	t = 0.27 d. f = 58, P = 0.78
5 min	93.2±7.8	93.9±7.6	t = 0.35 d. f = 58, P = 0.73
10 min	93.9±7.6	94.5±6.7	t = 0.32 d.f = 58, P = 0.75
15 min	95.3±7.5	96±6.45	t = 0.39 d.f = 58, P = 0.69
30 min	94.8±7.9	95.1±6.9	t = 0.16 d.f = 58, P = 0.87
45 min	94.5±9.3	94.9±9.2	t = 0.17 d. f = 58, P = 0.86
60 min	94.9±9.5	95.3±7.1	t = 0.37 d. f = 58, P = 0.71
Diastolic blood pressure			
Pre-induction	56.8±7.9	55.8±7.5	t = 0.50 d.f = 58, P = 0.62
Intubation	55.6±7.17	55.9±7.2	t = 0.16 d. f = 58, P = 0.87
Skin Incision	55.3±7.6	55.7±6.9	t = 0.21 d. f = 58, P = 0.83
5 min	55.4±6.9	55.8±6.7	t = 0.23 d. f = 58, P = 0.82
10 min	55.4±7.6	55.7±7.4	t = 0.15 d. f = 58, P = 0.87
15 min	54.7±7.7	55.1±6.9	t = 0.21 d. f = 58, P = 0.83
30 min	55.3±9.4	55.7±8.6	t = 0.17 d. f = 58, P = 0.86
45 min	55.6±9.2	55.8±9.06	t = 0.08 d. f = 58, P = 0.93
60 min	55.3±10.2	55.5±9.2	t = 0.08 d.f = 58, P = 0.94
Mean arterial pressures			
Pre-induction	68.6±7.7	67.7±7.1	t = 0.47, d.f = 58, P = 0.64
Intubation	67.8±6.8	68.2±6.7	t = 0.23, d.f = 58, P = 0.82
Skin Incision	67.5±7.2	68±6.5	t = 0.28, d.f = 58, P = 0.78
5 min	68±6.8	68.5±6.6	t = 0.29, d.f = 58, P = 0.77
10 min	68.2±7.1	68.6±6.7	t = 0.22, d.f = 58, P = 0.82
15 min	68.2±7.3	68.7±6.5	t = 0.28, d.f = 58, P = 0.78
30 min	68.4±8.5	68.8±7.7	t = 0.19, d.f = 58, P = 0.85
45 min	68.5±8.96	68.8±8.8	t = 0.13, d.f = 58, P = 0.89
60 min	68.5±9.7	68.8±8.2	t = 0.13, d.f = 58, P = 0.89
Respiratory rate			
Pre-induction	14.9+0.4	14.7+0.7	t = 1.36, d f = 58, P = 0.18
Intubation	14.6+0.6	14.7+0.6	t = 0.64, d.f = 58, P = 0.52
Skin incision	14.8+0.4	14.6+0.7	t = 1.35, d.f = 58, P = 0.18
5 min	14.8+0.5	14.9+0.4	t = 0.85, d.f = 58, P = 0.39
10 min	14.7+0.7	14.8+0.5	t = 0.63, d.f = 58, P = 0.52
15 min	14.8+0.5	14.7+0.6	t = 0.70, d.f = 58, P = 0.48
30 min	14.9+0.3	14.7+0.7	t = 1.4, d.f = 58, P = 0.15
45 min	14.7+0.7	14.8+0.5	t = 0.63, d.f = 58, P = 0.52
60 min	14.8+0.6	14.9+0.3	t = 0.82, d.f = 58, P = 0.42
SPO_2			
Pre-induction	99.9+0.3	99.9+0.3	t = 00, d.f = 58, P = 1
Intubation	99.9+0.4	99.7+0.6	t = 1.52, d.f = 58, P = 0.13
Skin incision	99.8+0.4	99.7+0.5	t = 0.86, d.f = 58, P = 0.4
5 min	99.9+0.4	99.8+0.5	t = 0.86, d.f = 58, P = 0.4
10 min	99.7+0.6	99.7+0.5	t = 00, d.f = 58, P = 1
15 min	99.9+0.3	99.7+0.6	t = 1.63, d.f = 58, P = 0.11
30 min	99.8+0.6	99.9+0.5	t = 0.70, d.f = 58, P = 0.49
45 min	99.7+0.5	99.7+0.5	t = 00, d.f = 58, P = 1
60 min	99.8+0.5	99.7+0.6	t = 0.70, d.f = 58, P = 0.48

shorter in the sevoflurane group (2.86±0.66 min) which corresponds to our study.[14]

In our study, time taken for following the verbal commands was significantly shorter with Group S when compared with Group P (P<0.01). In Group S it was 7.63+1.25 min

Table 4: Incidence of post-operative nausea and vomiting

Post-operative nausea and vomiting	Group P n (30)	Group S n (30)
Present	1 (3.33%)	5 (16.67%)
Absent	29 (96.67%)	25 (83.33%)
Chi-square and P value	χ^2=2.96, d.f=1, P=0.09	

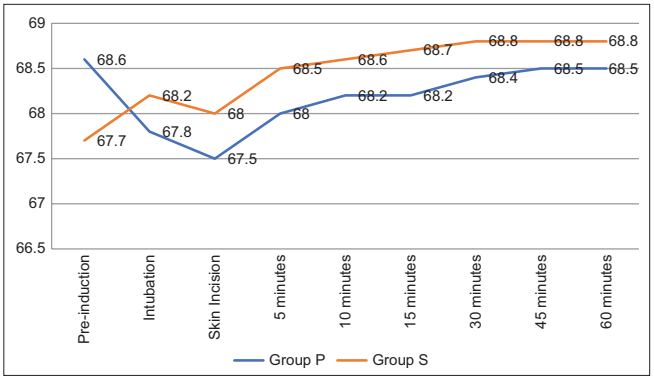

Figure 4: Comparison of mean arterial pressure in both the groups

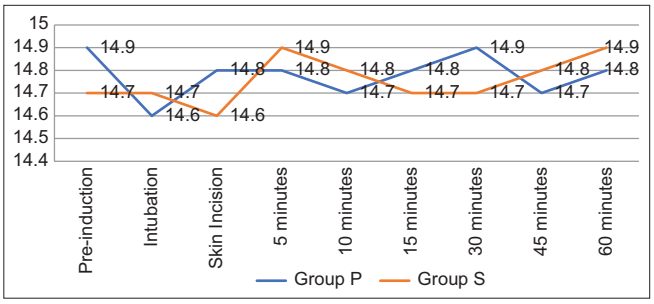

Figure 5: Comparison of mean respiratory rate in both the groups

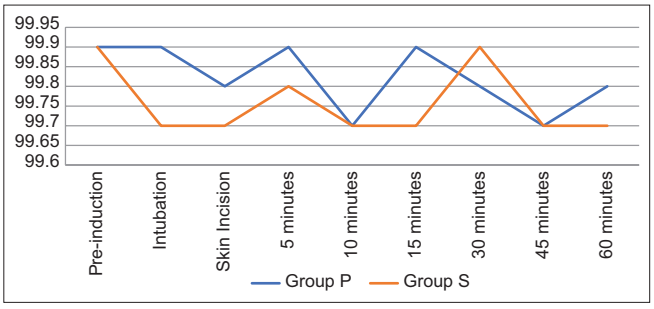

Figure 6: Comparison of mean SPO_2 levels in both the groups

whereas it was 10.13+1.28 min in Group P. Shorter mean time to following of verbal commands with sevoflurane may be due to rapid drug elimination. Singh et al. reported that time to follow verbal commands was significantly shorter in Group S (7.87±0.83 min) than Group P (11.88 ±1.30 min) which was similar to our study.[15] Orhon et al. found that Group S obeyed verbal commands earlier as compare to Group P (P<0.05) which corresponds with our study.[16]

In our study, the sevoflurane group took significantly shorter time for extubation when compared with the propofol group. The time was 8.67+1.24 min in Group S and 11.17+1.29 min in Group P (P<0.01). Shorter mean time to extubation with sevoflurane may be due to rapid drug elimination after tapering off sevoflurane. In a similar study Bharti et al. concluded that extubation time was not significantly different between Group P (8.5±4.3 min) and Group S (9.3± 3.7 min), which was not similar to our study.[17]

Time taken for orientation in Group P was 12.2+1.27 min and in Group S was 9.43+1.04 min. It was significantly shorter in sevoflurane group as compare to propofol group (P<0.01). Ebert et al. 67 found that patient orientation to his/her name was shorter in Group S (12. 2 min) than Group P (13.1 min), which was similar to our study.[18]

The intraoperative hemodynamic variables (heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure) were monitored in all patients and were maintained within baseline values in both the Group P and the Group S by adjusting the maintenance anesthetic concentration. There were no significant differences in the intraoperative hemodynamics of both the sevoflurane and the propofol groups. Ahila and Asokan found that the mean values of mean arterial pressure between the Group P and Group S were observed to be statistically not significant, which was similar to our study.[19]

The incidence of post-operative nausea vomiting was higher in Group S (16.67%) than Group P (3.33%) but it was statistically not significant (P=0.09). Tang et al. concluded that post-operative nausea and vomiting were much less in propofol group than sevoflurane group and statistically significant as well (P<0.05) which was similar to our study.[20]

Limitations of the study

One of the limitation of our study was that the study was done in young patients undergoing single type of surgery ie tonsillectomy. Studies on relatively older patients undergoing various surgeries are needed to further understand differences in intraoperative hemodynamics.

CONCLUSION

Sevoflurane as an anesthetic agent is associated with reduced time for spontaneous eye opening and for following verbal commands. Moreover, sevoflurane group took significantly shorter time for extubation when compared with the propofol group. Thus, we conclude that sevoflurane is a useful alternative to propofol in providing anesthesia where rapid emergence and recovery of cognitive functions are desired.

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Authors Contribution:
SA, AS - Concept and design of the study; interpreted the results, prepared first draft of manuscript and critical revision of the manuscript; **KM -** Statistically analyzed and interpreted; reviewed the literature and manuscript preparation; **NN -** Design of the study, statistically analyzed and interpreted, preparation of manuscript and revision of the manuscript; **SY -** Concept and coordination of the overall study.

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Study to assess proper timing of laryngoscopy in post-thyroid surgery patients to detect recurrent laryngeal nerve injury

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ABSTRACT

Background: Thyroid surgeries are commonly done nowadays for benign and malignant conditions. Recurrent laryngeal nerve palsy (RLNP) is an important and potentially catastrophic complication of thyroid surgery. The purpose of the study was to determine the impact of rigid endoscopy (Hopkins rod-lens telescope) performed at different time intervals on the diagnosis of RLNP in post-thyroid surgery patients. **Aims and Objectives:** To assess Proper Timing of Laryngoscopy in Post-thyroid Surgery patients to Detect RLN Injury. **Materials and Methods:** Rigid endoscopy was performed postoperatively at day 0 (T_0), at 2nd day post-op (T_1), and day 14 (T_2). For patients with RLNP, repeated examinations were performed at 2 months (T_3), 6 months (T_4), and 12 months (T_5). **Results:** The study included 50 patients of thyroid swelling with different diagnoses. Overall, 35 patients appeared for postoperative laryngoscopic examination of the vocal folds at our center, providing 61 nerves at risk. RLNP rate was 8.1% at T_0, 11.5% at T_1, 9.8% at T_2, 8.1% at T_3, 4.9% at T_4, and 3.3% at T_5. T_1 was significantly superior to all other time intervals in terms of diagnosis of RLNP but statistically not significant. **Conclusion:** Rigid endoscopy is essential for the detection of vocal cord paralysis after thyroidectomy. We report different time evaluation criteria of vocal cord morbidity with great and significant variability of results. Second day post-op inspection of the larynx (T_1) is suggested.

Key words: Laryngoscopy; Recurrent laryngeal nerve palsy; Thyroidectomy; Timing

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INTRODUCTION

The motor and sensory nerves of the larynx are derived from the vagus by way of its superior and recurrent laryngeal nerves (RLNs).[1] The most frequent and unpleasant complication of thyroid surgery is a RLN injury due to intraoperative damage. It may occur during surgery because of direct mechanical trauma, either with or without disruption. Injury to the RLN post thyroid surgery associated with hoarseness, impaired voice, dysphonia, dysphagia, aspiration, dyspnea, and in many cases to a life-threatening glottal obstruction. The reported incidence of temporary recurrent laryngeal nerve palsy (RLNP) ranges from 1.3% to 20%, while the incidence of permanent RLNP varies from 0% to 9%. These percentages are dependent on the type of surgery and thyroid gland disease.[2-5] RLN injury results in paralysis of all the intrinsic muscles of the larynx except the cricothyroid muscle which is supplied by the superior laryngeal nerve (SLN). There is an inability to abduct and adduct the vocal folds.[6] RLN paralysis rate is higher in cancer, Graves disease, reoperation, sub sternalgoiter, in less experienced surgical centers, and in patients in whom the inferior laryngeal nerve could not be identified and or monitored during operation.[7-10] The most frequent published mechanism of RLN injury is over-stretching of the nerve at the region of Berry's ligament clamping or transecting of the nerve. The true overall injury rate of RLN is not yet delineated for several actual reasons:

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- No routine audit by centers performing thyroid surgery - not all patients infact undergo a systematic laryngeal examination in the postoperative period.[11,12]
- Lack of reliability of clinical symptoms in vocal cord paralysis.
- There is considerable variation in the reported frequency of RLNP rates after thyroid surgery due to the different methods of diagnosing RLNP, i.e. indirect laryngoscopy versus rigid endoscopy versus fiber-optic nasolaryngoscopy (FNL) versus video stroboscopy, each of which have significant different sensitivities and specificities.[13]

Rigid endoscopy offers improved visualization of the larynx through better illumination, higher magnification, and wider and deeper fields of vision.

The angled endoscopes allow better perspectives of the ventricle, free edge, and under the surface of the vocal cord.[14] Assessment of vocal cord functions (VCFs) with a laryngoscope is of great importance in the preoperative and postoperative evaluation of patients undergoing thyroidectomy.[15] Pre-operatively, VCF detects an existing RLNP from local invasion of the nerve by extra-thyroidal cancer extension or regional lymph node metastases.[16,17,18] Postoperative assessment of VCF documents a well preserved VCF, or an iatrogenic RLN injury, and yet the benefits of speech, rehabilitation, steroid, and surgical treatment. There is currently a lack of consensus to support the proper timing for the postoperative laryngoscopy that is reliable to diagnose RLNP.

Aims and objectives

To assess Proper Timing of Laryngoscopy in Post-thyroid Surgery patients to Detect RLN Injury.

MATERIALS AND METHODS

This prospective study "Study to assess Proper Timing of Laryngoscopy in Post-thyroid Surgery patients to Detect RLN Injury" was conducted from 30 Nov 2011 to 30 Nov 2013 in 50 patients undergoing laryngoscopy in post thyroid surgery at different time intervals. The written and informed consent was obtained from each patient in advance for consecutive laryngoscopy. Pre- and post-operative follow-up include for all patients to check vocal cord mobility by laryngoscopy. Every patient in the study was evaluated on the basis of brief history, general and local examinations including indirect laryngoscopy and 900, 700 rigid endoscopy. Indirect mirror laryngoscopic findings were confirmed by rigid endoscopy (Hopkins rod-lens telescope- Figure 1)

Inclusion criteria

1. All patient of thyroid swelling.
2. All cases of different thyroid surgeries.
3. Patients who have given written informed consent for laryngoscopy, pre and post thyroid surgery.
4. Patients who have given written consent for follow up.

Exclusion criteria

1. Established preoperative injury to the laryngeal nerves.
2. Intraoperative finding of tumour involvement of RLN.
3. Patients who were lost during the follow-up study.

70° Or 90° Hopkins rod-lens telescope/endoscope

A rigid telescope with an angled lens of 70° or 90° can be passed through the mouth to the oropharynx to view the larynx. Twenty centimeters are often a comfortable telescope length for the endoscopist. The laryngeal examination with a 70° rigid endoscope is conducted with the patient bending slightly forward from the hips while maintaining a straight back. The neck and chin are extended, and the tongue is protruded. The examiner wraps the tongue in gauze and holds it gently during the examination. The endoscope is advanced just under the uvula or between the uvula and faucial pillars until the epiglottis is visualized. Turning the endoscope tip to face the cheek during insertion, to prevent tongue residue from coating the lens, might keep the lens cleaner. Having the patient vocalize a sustained "hey" lowers the tongue base, facilitating placement. The patient is then instructed to sustain "ee," which moves the epiglottis anteriorly for a better view of the vocal folds. The examiner might need to flex the wrist to tilt the endoscope tip inferiorly. The angle can be varied for differing levels of magnification and differing fields of view. The patient is then guided through the examination tasks listed in the following "Assessment" section. Examination with the 90° endoscope is similar, but the patient does not need to bend forward or extend the neck. Another difference is the angle; the tip of the 90° scope is positioned with minimal tilt so that the light is parallel to the surface of the vocal folds. This type of endoscope is often preferable for viewing the larynx when a wider viewing angle is desired. A longer lens or a zoom lens might be necessary for adequate visualization of vocal fold details. Children as young as 6 or 8 years of age may be able to cooperate for this examination.

Laryngoscopy was performed at 24–48 h before operation (T_x). Postoperatively patients were evaluated for RLN injury by laryngoscopy on the same day (T_0), on day 2 (T_1) and on day 14 (T_2).

RLNP is defined as newly discovered reduction in the movement of vocal folds after surgery compared with the

preoperative status. For patients with postoperative cord palsy, repeated examinations were performed periodically at 2 months (T_3), 6 months (T_4), and 12 months (T_5). When laryngoscopy was found normal at T_0, T_1, and T_2 examination, the patients were not taken for further laryngoscopy.

Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983.

Statistical analysis

Findings were noted and tabulated. Measurement of the RLNP rate was based on the number of nerves at risk (NAR). All data were analyzed statistically using statistical package for the social sciences 20 and Chi-square test for differences in postoperative RLNP rate and recovery days. Test was significant when $P<0.05$. Then conclusions were drawn after analysis.

RESULTS

The present study was carried over a period of 2 years in the Department of Otorhinolaryngology, J. N. Medical College and Hospital A. M. U. Aligarh. The study included 50 patients of thyroid swelling with different diagnosis. All 50 patients scheduled for thyroidectomy underwent preoperative evaluation of the vocal folds. At pre-operative laryngeal examination, we found two alterations of vocal folds movement in 50 patients (4%). Based on the exclusion criteria, these two patients ruled out the analysis.

Complete follow-up was available for 96% of patients (48/50). Five patients were unwilling to accept further laryngeal re-examination, and they were asymptomatic. Moreover, eight other patients were loss during the follow-up study.

Overall, 35 patients appear for post-operative laryngoscopic examination of the vocal folds at our center, providing 61 NAR for examination. Table 1 summarizes the distribution of epidemiological characteristics of patients, thyroid pathology, and procedures.

The RLN was virtually identified in all cases. No bilateral vocal cord paralysis occurred. Overall permanent RLNP occurred in 3.2% (n=2), while the temporary RLN injury in 8.1% (n=5). The rate of RLN morbidity shows a considerable variation due to the different time intervals of laryngoscopy. The rate of RLNP was 8.1% at T_0 (5 out of 61 NAR), 11.5% at T_1 (7 out of 61 NAR), 9.8% at T_2 (n=6), 8.1% at T_3 (n=5), 4.9% at T_4 (n=3), and 3.3% at T_5 (n=2), according to different time intervals of laryngoscopy in the postoperative period.

Table 1: Preoperative characteristics and operative parameters in 35 patients undergoing thyroidectomy

Parameters study group	
Age (years)	35.89 (18–58)
Women (N)	25
Men (N)	10
Lobectomy	9 (25.7%)
Total thyroidectomy	2 (5.7%)
Subtotal thyroidectomy	17 (48.6%)
Revised near total thyroidectomy	2 (5.7%)
Near-total thyroidectomy	5 (14.3%)
Nerves at risk	61
Preoperative diagnosis	
Multinodular goiter	9 (25.7%)
Papillary carcinoma	2 (5.7%)
Goitre with left complex cyst 1	(2.9%)
Left thyroid cyst 2	(5.7%)
Recurrent multinodular goiter	2 (5.7%)
Simple colloid goiter	13 (37.1%)
Left solitary nodular goiter	2 (5.7%)
Right solitary nodular goiter	3 (8.6%)
Right thyroid cyst	1 (2.9%)
Hyperthyroidism	2 (5.7%)

In our study, the rate of detection of RLNP at T_1 (day 2) was superior as compared to other time intervals of laryngoscopy, but it is statistically insignificant ($P>0.05$).

DISCUSSION

Thyroid surgeries are commonly done nowadays for benign and malignant conditions. There is a need to know the complications of surgeries for the post-operative management of the patients to prevent morbidity and mortality. RLNP is an important and potentially catastrophic complication of thyroid surgery. Voice dysfunction after thyroidectomy is not rare and is generally reported in terms of RLN or SLN injuries. However, voice dysfunction can occur without laryngeal nerves injuries. Prompt recognition of causes of dysphonia is essential so that relevant therapeutic decision allows early management. During recent years, intraoperative nerve monitoring has been introduced to decrease the frequency of nerve injuries during thyroid surgery. It has been argued that in expert hands, the risk is very low.[17,18]

Pre and post-operative laryngoscopy is required to detect RLN injury accurately. Pre-operative vocal cord evaluation will ensure adequate diagnosis and documentation, aid surgical planning and consent, and reduce any medico-legal implications. In our study 50 patients scheduled for thyroidectomy underwent preoperative evaluation of the vocal folds, we found alterations of vocal folds movement in 2 patients (4%).

The result of our study was also in accordance with the study conducted by Sayyahmelli et al.,[18] who studied 100 patients

scheduled for thyroidectomy, there were 89 cases who had benign disease of thyroid and 11 cases of malignancy. Modification of voice and impaired vocal fold motion were seen in 11 and seven patients before operation, respectively, and emphasized the need of preoperative examination of the larynx of patients undergoing surgery for thyroid gland. Likewise, the absence of abnormality in voice would not accurately rule out the probability of vocal fold or laryngeal nerve lesions. This is the second study done to evaluate the impact of time interval of the post-operative laryngoscopy for the diagnosis of RLN injury after thyroid surgery. The potential, useful, and proper timing of laryngeal inspection for the diagnosis of RLNP is not well documented in literature. This study identifies that the wide variation of rates of RLNP is dependent even upon the day of vocal cord assessment in the early post-operative period. The post thyroidectomy laryngoscopic finding in our study (Table 2) is that rate of detection of RLNP is superior at T1 (2nd post-operative day) as compared to other days, i.e., T0 (at the day of thyroidectomy), T2 (2 weeks), T3 (2 months), T4 (6 months), and T5 (12 months). The rate of detection of RLNP noticeably reduced as the time interval of laryngoscopy increased. The reason for the superior sensitivity of RLNP rate detection at T_1 as compared to other days (i.e., T_2, T_3, T_4, and T_5) may be associated with the extent of RLN injury, varying in its severity from neurapraxia to axonotmesis and neurotmesis. Studies showed that RLNP process subdues from the very 1st days post-operative.[18]

Wagner and Seiler,[19] Chiang et al.,[20] and Snyder et al.,[21] noted that their cases of temporary paralysis resolved in starting early from the 3rd post-operative day.

Karlan et al.,[22] described cases of transient paralysis with recovery ranging from the 1st week postoperative. In fact, partial injuries (neurapraxia) are much more common than complete transaction (neurotmesis).

Chiang et al.,[23] reported a recovery from temporary RLNP from 3 days to 4 months (mean, 30.7 days). While after neurotmesis has occurred, no such recovery would be seen. Therefore, most studies suggest that a follow-up period of 12 months minimum is needed to assess voice function after if dysphonia is detected after thyroid surgery.

The reason of the superior sensitivity of T_1 compared to T_0 may be associated to patient's poor compliance, self-adherence, and the degree to which he/she correctly follows medical advice during the laryngoscopy early after extubation (T_0) and early complications of intubation, i.e. vocal cord congestion and edema hinder correct assessment of VCFs. Factors that may decrease patient's compliance in T_0 include patient feeling ill, limitations of patients activities due to the anesthesia state, acute illness, local pain, poor analgesia support, purpose of laryngoscopy not clear, instructions for laryngoscopy not clear, physical difficulty in complying laryngoscopy, and unattractive/unpleasant examination. This result of our study was also in accordance with the study conducted by Dionigi et al.,[24] (2010) performed FNL of 434 post thyroid surgery patients at different time intervals. They recorded rate of RLNP 6.4% at day 0 (T_1), 6.7% at day 2 (T_2), 4.8% at 2 week (T_3), 2.5% at 2 months (T_4), 0.8% at 6 months (T_5) and 0.7% at 12 months (T_6). They suggested day 2 (T_2) post-operative FNL is superior to detect RLN injury.

Most European, as well as American thyroid association's guidelines, recommend laryngoscopy only for voice dysfunction persisting beyond 2 weeks after thyroidectomy.[25,26]

Studies that evaluated the rates of RLN injury after a thyroid surgery reported considerable variation in the reported frequency of vocal cord palsy rates due to the different reasons to perform laryngoscopy postoperatively, i.e., to all patients or only patients with impaired voice register. Moreover, due to different periods of time (as at extubation, hospital discharge, and weeks after surgery) of which we now demonstrated have significant different sensitivities and specificities.[15] All patients should undergo pre- and post-operative laryngeal examination if we need to appreciate the true rate at which RLN injury occurs.

It is impossible to diagnose RLNP without performing the laryngeal examination, and also to use the benefits of speech, steroid therapy, surgery, and rehabilitation.[27-30] Uniform and standard criteria for evaluating the VCF after surgery are certainly needed to plan an effective and early treatment and also to be able to compare the results among different centers.

In our study, we noted permanent RLNP in 3.3% of thyroid surgeries, temporary RLN injury in 8.2% while none had bilateral RLNP. We have noted that approximately 57% of those RLNP recovered within 6 months, and 71% in 12 months. Thus, permanent RLN paralysis may be diagnosed on the basis of serial laryngeal examinations between the period of 6 and 12 months after a thyroid surgery. Therefore, through our study, we suggest follow-up period of 12 months minimum to assess the voice function after thyroidectomy surgery, if any dysphonia is detected (Figure 2). This is similar with other studies where the period of follow-up for RLNP after a thyroid surgery was 1 year.[2]

Table 2: Chi-square and *P* values of rate of detection of RLNP at t_1 (day 2) as compared to other days of laryngoscopy

Timing of Laryngoscopy	P value	Chi-square value (χ^2)	Degree of freedom
T_0 (day 0)	0.543	0.370	1
T_2 (day 14)	0.769	0.086	1
T_3 (2 months)	0.543	0.370	1
T_4 (6 months)	0.322	0.980	1
T_5 (12 months)	0.166	1.919	1

RLNP: Recurrent laryngeal nerve palsy

Figure 1: 70° Hopkins rod-lens telescope/endoscope

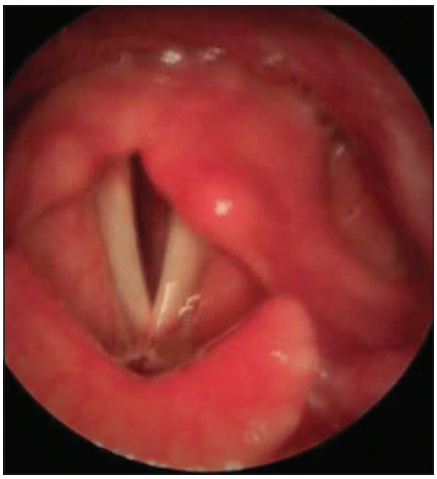

Figure 2: 90° Endoscopic view of left vocal cord palsy/left recurrent laryngeal nerve injury (Post-operative)

Jeannon et al., shows in their study that average rate of temporary RLNP after thyroid operations is 9.8%, and of permanent RLNP is 2.3%. According to the method of examining the larynx, the RLNP rate varied and it ranged from 26% to 2.3%. Most of the studies which are reviewed recommend a period of follow-up till 1 year to assess and evaluate RLNP.

Limitations of the study

The present study has some limitations. The sample size was small.

CONCLUSION

Although the incidence of laryngeal nerve palsy after thyroidectomy is low, the condition has to be promptly recognized and investigated by the surgeon. The variable symptoms that occur are cough, dysphonia, dysphagia, and dyspnea. Their intensity and association are variable. We propose different interval time evaluation criteria of vocal cord mobility post-thyroid surgery. The rate of RLNP is influenced by the "timing" of the postoperative laryngoscopy. We conclude that proper timing of laryngeal inspection for the diagnosis of RLNP is on 2nd post-operative day.

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Single incision laparoscopic appendectomy: A prospective study

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ABSTRACT

Background: Appendicitis is one of the common pathologies encountered in surgical practice. Except in minority of the cases, the treatment is usually surgical. Till recent past, open appendectomy has been the procedure of choice for appendicitis. With increasing expertise in laparoscopic surgeries more and more surgeons are utilizing the laparoscopic approach for appendectomy. Laparoscopic surgeries have distinct advantages such as less surgical trauma, improved and quick postoperative recovery, and esthetic results. Single-incision laparoscopic surgery (SILS) is rapidly gaining acceptability in young population because of its cosmetic advantages. Moreover, these surgeries also avoid the risk of port-site hernias and the possibility of wound infection. **Aims and Objective:** The purpose of this study is to present our initial experience with this surgery using a single incision laparoscopic appendectomy (LA) using conventional instruments. **Materials and Methods:** This was a prospective cohort study conducted in the department of surgery of a tertiary care medical college situated in an urban area. The duration of the study was 2 years. All adult patients diagnosed to be having uncomplicated appendicitis and undergoing appendectomy by SILS were included in this study on the basis of a predefined inclusion and exclusion criteria. Pre-operative data collected included age, sex, weight, duration of complaint, concomitant medical conditions (like ischemic heart disease, chronic obstructive airway disease, diabetes mellitus, pancreatitis, and liver cirrhosis) and previous upper or lower abdominal surgery. All patients were treated by SILS except 1 patient in whom the procedure was converted to open surgery. Mean surgical time, Intraoperative procedure details and postoperative complications were studied in all the cases. $p < 0.05$ was taken as statistically significant. Statistical analysis was done using SSPS 21.0 software. **Results:** Out of 30 patients in this study 26 patients were female and 4 patients were male. The male to female ratio was found to be 1:6.15. Mean age of studied cases was found to be 26.2 years. Operative time required for the first 15 cases in an average was 120.00 min however it was reduced for the next 15 cases was 73.73 min. Overall time required in an average was 96.86 min. Out of 30 cases, The procedure was completed with Single Incision LA in 23 Patients, i.e., 76.6 %. In the initial cases, we started with two 5 mm and one 10mm port. To reduce crowding we replaced the 5 mm port to 3 mm port. The 10 mm port was also replaced by 5 mm in the past few cases in 1 patient the procedure was converted to open surgery. The analysis of postoperative complications showed that five patients had Post-Operative wound Infection. One patient had post-operative peritonitis. **Conclusion:** SILS is a feasible and safe surgical method for appendectomy and is being increasingly preferred particularly by young patients due to its excellent cosmetic results.

Key words: Single-incision laparoscopic surgery; Acute appendicitis; Appendectomy; Cosmetic results

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INTRODUCTION

Appendicitis is one of the common causes for which surgical consultations are sought. It usually presents with abdominal pain (periumbilical to begin with and followed by right lower quadrant pain), nausea, anorexia, and vomiting.[1] On clinical examination these patients have classical right lower quadrant tenderness. It can reliable

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be diagnosed by ultrasound examination which is a quick and reliable imaging technique.[2] In some cases where the diagnosis can't be established or ruled out on the basis of ultrasound a computerized tomography may be required for diagnosis.[3] It is also useful for diagnosis in pediatric patients in whom it's difficult to demonstrate inflamed appendix particularly in children who remain non-co-operative during ultrasound scanning.[4]

Once the diagnosis is established management is usually surgical and appendectomy has been the surgical procedure of choice once the diagnosis is established.[5] Till recent past Open appendectomy has been the procedure of choice for appendicitis. With increasing expertise in laparoscopic surgeries more and more surgeons are utilizing the laparoscopic approach for appendectomy.[6] Laparoscopic surgeries have distinct advantages such as less surgical trauma, improved and quick postoperative recovery, and aesthetic results. Following laparoscopic appendectomy (LA), the patient is able to quickly return to performing everyday activities and there is a significant reduction in hospital stay following surgery as compared to patients who have undergone appendectomy by open surgery.[7]

Minimally invasive surgical approaches used for appendectomy include traditional LA, Single-incision laparoscopic surgery (SILS), natural orifice transluminal endoscopic surgery (NOTES), and mini laparoscopy-assisted natural orifice surgery (MANOS).[8] In conventional LA usually 3 incisions are taken whereas in SILS, as name suggests, only 1 incision is used to perform appendectomy. SILS is usually done by single transumbilical incision. Relatively newer techniques such as NOTES and minilaparoscopy-assisted natural orifice surgery (MANOS) utilizes natural orifices such as vagina to perform appendectomy in an effort to avoid any visible scar.[9] It also does have advantages such as reduced surgical pain, reduced analgesic requirement, faster recovery, absence of risk of hernia formation, and reduced risk of surgical site infection.[10]

SILS is rapidly gaining acceptability in young population because of its cosmetic advantages. Moreover, these surgeries also avoid risk of port-site hernias and the possibility of wound infection. In expert hands, the scar is practically hidden within the umbilicus leaving no visible scar mark of surgery. Although SILS has many advantages it definitely is a more challenging procedure as compared to open or even conventional LA. Moreover, the duration of surgery for SILS is longer as compared to conventional laparoscopic surgery and this needs to be carefully considered while selecting patients for SILS. Moreover, single incision surgery provides a compromised view and locomotive field for surgeon which is one of the biggest challenges for surgeons.[11]

The purpose of this study is to present our initial experience with this surgery using a single incision LA using conventional instruments.

Aims and objectives

The aim of this study was to present a minimally invasive technique for appendectomy and to study the complications in patients undergoing single incision laparoscopic appendectomy (LA) using conventional instruments.

MATERIALS AND METHODS

This was a prospective cohort study conducted in the department of surgery of a tertiary care medical college situated in an urban area. The duration of the study was 2 years. All adult patients diagnosed to be having uncomplicated appendicitis and undergoing emergency as well as elective appendectomy by SILS were included in this study on the basis of a predefined inclusion and exclusion criteria. The institutional ethical committee approved the study and written informed consent was obtained from all the patients.

The study participants were interviewed and examined according to the preformed and pretested proforma and then operated as per the defined procedure. Pre-operative data collected included age, sex, weight, duration of complaint, concomitant medical conditions (such as ischemic heart disease, chronic obstructive airway disease, diabetes mellitus, pancreatitis, liver cirrhosis), and previous upper or lower abdominal surgery. Routine laboratory investigations such as complete blood count, liver function tests, blood sugar, blood urea, and serum creatinine were done in all the cases. The diagnosis was made on the basis of history and clinical examination. The diagnosis was confirmed by ultrasound examination. In cases where there was significant probe tenderness and radiologist could not find inflamed appendix on ultrasound a computerized tomography was done for confirmation of diagnosis.

Appendectomy done was either emergency appendectomy or elective appendectomy. Patients in whom elective appendectomy was done Patients were managed by Oschner Sherren regime consisting of indoor management including intravenous antibiotics, intravenous fluids, nil oral status, and frequent clinical examination to rule out spreading peritonitis, which is an indication for abandoning the conservative treatment. In these cases, SILS appendectomy was done after 6 weeks. If converted

to conventional laparoscopic/open method, the causes of conversion, step at which converted, time after which conversion was done and the number of additional ports used were noted.

Surgical procedure

All patients were administered general anesthesia and were given supine position. A prophylactic dose of antibiotics (ciprofloxacin 200 mg and metronidazole 500 mg iv) was given at induction. The operating surgeon stood on the left side of the patient along with the assistant. A vertical incision around 1.5–2 cm was made through the umbilicus, Incision was deepened and the peritoneum was opened under direct vision (Hasson technique). A 10 mm port was introduced. CO2 insufflation was done and pneumoperitoneum was created (12–14 mm hg). A right-sided 5 mm and left-sided 3 mm working ports were introduced through the same incision on either side of the optical port (Mickey Mouse Technique). Ports were placed at different levels to maximize the working space and instrument range of motion within the peritoneal cavity. Table was placed in Trendelenburg position with left-sided tilt.

Mesoappendix was then cauterized using bipolar cautery. Two roeders knot was applied at the base of the appendix and one above it and the appendix was cut in between 2nd and 3rd roeders knots. Lateral peritoneal dissection with caecal mobilization was done in case of non-visualization of the appendix. The appendicular base was dissected first in case of non-visualization of the appendicular tip in some cases. Epidural needle was inserted in the right iliac fossa and prolene loop was made and inserted to suspend the appendix (Puppeteer technique) when required. The appendix was removed from the 10 mm port after hemostasis was confirmed. Suction and Irrigation were done when required to clear the remaining debris and collection.

Ports were removed, subcutaneous layer closed with port closure vicryl and Skin closed with nylon 3–0. All port sites were infiltrated with 2cc of 0.25% Bupivacaine, just before closure of port sites. All patients received an intra-operative dose of 75 mg Diclofenac. Cleaning and dressing were done.

Patients were kept nil by mouth until evening and were supplemented by intravenous fluids. Oral was allowed by evening unless contraindicated. Post-operative pain was measured using 0-10 Numerical Pain Rating Scale as described by Pasero.[12] The pain scale involved asking the patient to estimate their pain severity as a number "0" being no pain and "10" being worst possible pain at post-operative time of 6 h.

All patients received injectable Diclofenac 75 mg post-operatively once at 8 h until the patients were allowed orally then oral diclofenac 50 mg for 3 days in bid dosage. Patient was discharged when he/she was suitable for discharge, which was evaluated clinically. Post-operative hospital stay was calculated in days.

Post-operative check dressing was done on day 3. Suture removal was done on day 7. Patients were followed up until 2 months with a regular OPD checkup once in 15 days. Patients were then assessed for post-operative complications like intra-abdominal collection, peritonitis, wound infection, seroma formation, wound gape, scar pain, scar hypertrophy, port site hernia, and any mortality if any. Statistical analysis was done using SSPS 21.0 software.

Inclusion criteria

1. All adult patients diagnosed to be having uncomplicated appendicitis and undergoing emergency as well as elective appendectomy by SILS
2. Those who gave informed written consent to be part of the study.

Exclusion criteria

1. Those who refused consent
2. Age less than 18 years
3. Appendicular perforation or abscess
4. Patients on analgesics for chronic pain likely to hinder assessment of postoperative pain.

RESULTS

This study was carried out in the Department of Surgery, of our institute. In this study, 30 patients of appendicitis were treated by Single Incision LA. Of 30 patients in this study, 26 patients were female and four patients were male. The male-to-female ratio was found to be 1:6.15 (Figure 1).

Most of the patients undergoing Single Incision LA were in the age group 30–39 years (33.33%), followed by 20–29-year age group (30%) and 10-19 age group (30%) each. The mean age of studied cases was found to be 26.2 years (Table 1). Single Incision LA was performed for Acute Appendicitis in two patients. Interval Appendectomy was performed in 28 patients (Table 1).

Table 1: Distribution of patients according to age group

Age in years	No of Patients	Percentage
10–19	9	30
20–29	9	30
30–39	10	33.33
>39	2	6.67

Operative time required for the first 15 cases in an average was 120.00 min however it was reduced for the next 15 cases was 73.73 min. The overall time required in an average was 96.86 min. The minimum time required to perform SILS was 40 min and the maximum time was 175 min (Table 2).

Of 30 cases, 16 cases were completed using Single-incision with 3 ports. In six cases a prolene loop was inserted with the help of an epidural needle in the right iliac fossa to suspend the appendix. In one case a 2 mm alligator grasper was used through the suprapubic region to suspend the appendix. In six cases an additional 5mm/3mm port was used during the procedure. In one case single incision LA was converted to open appendectomy due to non-visualization of the appendix. Of 30 cases, the procedure was completed with single-incision LA in 23 patients, i.e., 76.6 %. In the initial cases, we started with two 5 mm and one 10mm port. To reduce crowding we replaced the 5 mm port to 3 mm port. The 10 mm port was also replaced by 5 mm in the past few cases. The 10 mm just being finally used only for retrieval. This solved the problem of crowding at the umbilicus. However, it was observed that it was difficult to hold a turgid appendix with 3 mm instrument. In cases where an initial 10 mm port was used for dissection Appendix was retrieved from the 10 mm port. In cases where 10 mm port was not used to begin with, one 5mm port was replaced by 10 mm port at the end, and an appendix was retrieved from this port. We used in couple of cases, a technique where the long end of vicryl of 3rd roeders knot stays out of 5mm port and a thread was passed through 10mm port blindly and the free end of the thread is railroaded through the 5 mm port and tied and bought out of 10 mm port hence the specimen can be brought out from 10 mm port. This obviated the need of 5 mm telescope. In 16 cases appendix was retrocaecal and hence lateral peritoneal dissection with caecal mobilization was done in these cases. In the remaining 14 cases inflamed appendix could be approached without caecal mobilization. Meso appendix was dissected with bipolar cautery in most cases 0.10 mm and 5 mm clips were used in few cases. Harmonic Scalpel was used in one case (Figure 2 and Table 3).

Of 30 cases, five patients had post-operative wound infection. One patient had post-operative Peritonitis for which re-exploration was done on post-operative day 2 and peritoneal suction and irrigation was done (Table 4).

Table 2: Operative time in studied cases

No of cases	Time in minutes
In first 15 cases	120.00
In next 15 cases	73.73
Overall average time in 30 cases	96.86

Out of 30 patients, 18 patients were discharged on day 2 which accounts for 60% of total patients. Nine patients were discharged on day 3, whreas 2 patients were discharged on day 4. One patient was discharged on day 14. The mean average of hospital stay is 2.83 days (Table 5).

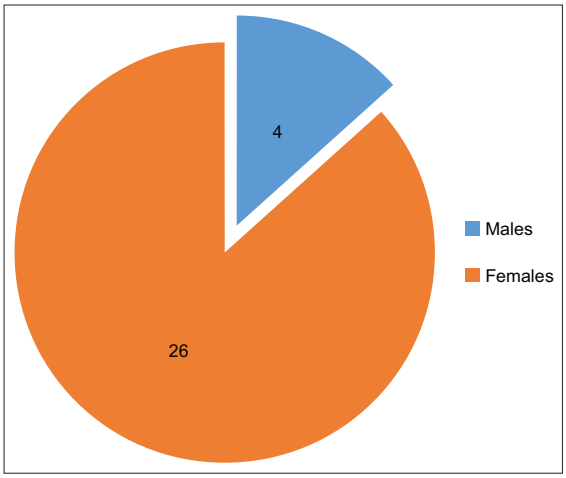

Figure 1: Gender distribution of studied cases

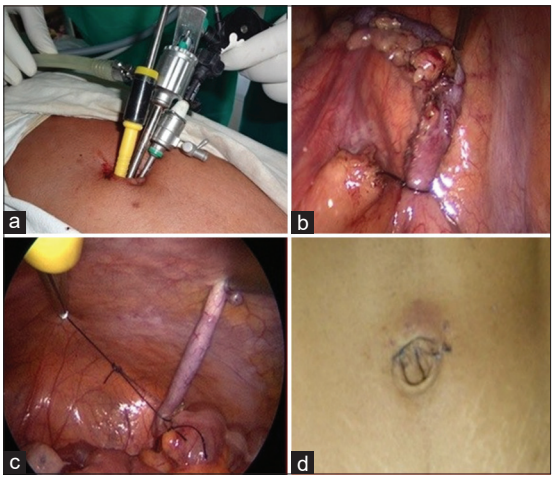

Figure 2: (a-d) Photographs showing (Clockwise from left upper corner) Two 5 mm and one 3 mm ports, Appendix with 1st Roeders Knot, Appendix with 2nd Roeders Knot and hardly visible post-operative scar

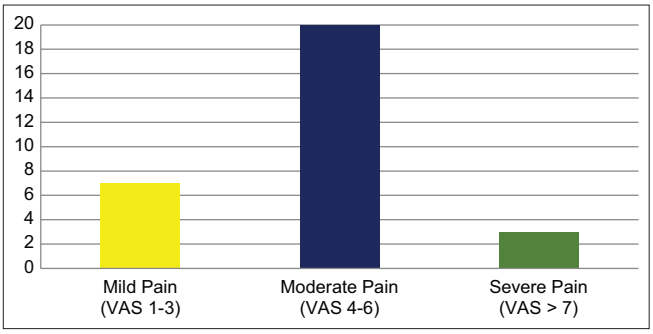

Figure 3: Severity of post-operative pain

Table 3: Intraoperative procedure details

Procedure details	Number of cases	Percentage
Completed using 3 ports in single incision	16	53.33
Additional rescue port	6	20.00
Usage of Prolene loop	6	20.00
Usage of 2 mm Alligator forceps	1	3.33
Conversion to open	1	3.33

Table 4: Post-operative complications in studied cases

Post-operative complications	No of patients
Wound Infection	5
Peritonitis	1

Table 5: Hospital stay of the patients

No of days	No of patients	Percentage
2	18	60
3	9	30
4	2	6.66
>4	1	3.34

Pain was measured at the end of 6 h post-operative time using 0–10 numerical pain rating scale (VAS score). Out of 30 cases, 7 patients (23.33%) were found to have mild pain (VAS score 1–3) whereas moderate pain (VAS score 4–6) was seen in 20 (66.66%) patients. Severe pain (VAS >6) was seen in 3 patients (10%) (Figure 3).

DISCUSSION

In this study, 30 patients of appendicitis treated by Single Incision LA were included. IN our study there was a female preponderance with a M:F ratio of 1:6.15. Frutos et al.[13] conducted a study of 73 patients with acute appendicitis treated by SILS. In this study, the authors found that None of the patients required conversion to conventional laparoscopy. The mean surgical time was 40 ± 14 (16–80) minutes. There were no complications during or after the surgery. The mean post-surgical pain score was 3 ± 1 (1–7) and the mean hospital stay was found to be 18 ± 7 (9–42) hours. The gender distribution of studied cases showed that there was a female preponderance with M: F ratio being 1:1.43. This female preponderance was similar to our study. Some other authors such as Addiss et al.[14] reported a male preponderance in cases of acute appendicitis.

The mean age of studied cases in our study was found to be 26.2 years. Sonawane et al. conducted a study of 138 patients of acute appendicitis.[15] The authors found that the mean age of studied cases was 27.41 years. Similarly, Resutra et al.[16] in their study of 400 patients of acute appendicitis treated by open as well as LA found the mean age of studied cases to be 35 years.

In this study, the mean operative time for 30 patients is 96.86 min. In the first 15 cases the mean operative time was 120.00 min however in the next 15 cases it has come down to 73.73 min. This has been mainly attributed to the learning curve for single-incision laparoscopic procedure range (40–175 min). In Kim et al.[17] study, the mean operative time was 61.3 min (range 24–120 min). In Chiu et al.[18] study, the mean operative time was 58 min (33–107 min). The operating surgeon's experience is one of the important factors apart having a major impact on mean operative time in cases of laparoscopic surgeries.

In this study, out of 30 cases, 16 cases were completed by using 3 ports. In six cases a prolene loop was inserted with the help of epidural needle in the right iliac fossa to suspend the appendix. In one case a 2 mm alligator grasper was used through the suprapubic region to suspend the appendix. In 6 cases an additional 5 mm/3 mm port was used during the procedure. In One case Single incision LA was converted to open appendectomy due to non-visualization of the appendix. Out of 30 cases, the procedure was completed with Single Incision LA in 23 Patients, i.e., 76.6 %. In a similar study by Uday et al.[19] study, all 32 patients were completed with single incision laparoscopic procedure, i.e., 100%. In this study, a SILS port was used in all cases.

In this study out of 30 cases, five patients had Post-Operative wound Infection. One patient had post-operative Peritonitis for which re-exploration was done on post-operative day 2 and abdominal wash was given. In a similar study by Bhatia et al.[20] study, out of 17 cases, no post-operative complication reported.

Limitations of the study

Small number of cases and absence of a comparator group were limitations of this study. A well designed large comparative study would give further insights into advantages of Single incision laparoscopic appendectomy over conventional methods.

CONCLUSION

SILS is a safe procedure having excellent cosmetic results. With increasing experience, the operative time goes down and difficulties of crowding at the umbilicus can be reduced considerably using small size ports.

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Authors Contribution:
NPM- Concept and design of the study; interpreted the results, prepared first draft of manuscript and critical revision of the manuscript, Statistically analyzed and interpreted; reviewed the literature and manuscript preparation; Design of the study, statistically analyzed and interpreted, preparation of manuscript and revision of the manuscript, Concept and coordination of the overall study.

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The comparative study of quality of life among working women and homemakers taking care of psychiatric patients presenting in a tertiary care hospital, Patna

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ABSTRACT

Background: In India, women are twice more likely to become caregivers than men. The quality of life (QOL) is the ability level to which an individual is healthy and able to enjoy life. **Aims and Objective:** To assess and compare QOL among homemaker women and working women giving care to patients suffering from psychiatric illnesses. **Materials and Methods:** This hospital-based, cross-sectional study was conducted on the caregivers who were recruited from out-door patient department of Psychiatry department of Patna Medical College and Hospital, Patna from January 1, 2021, to June 31, 2021. Women who were 30–55 years old, working or homemakers, and who were taking care of psychiatric patients diagnosed with Schizophrenia and Bipolar affective disorder of either sex. Caregivers were first degree relatives of patients. The estimated sample size was 140 (Group 1 = 70 homemaker women and Group 2 = 70 working women). Sociodemographic data were recorded using Sociodemographic Performa 1 and QOL was assessed using World Health Organization (WHO)-QoL-BREF. **Results:** WHO-QOL domain mean score for physical, psychological, social, and environmental of Group 1 was 12.42, 11.60, 12.24, 12.62 whereas 14.46, 13.28, 11.28, and 12.28 of Group 2 with statistically significant difference ($P < 0.05$). **Conclusion:** In physical and psychological domain of QoL, working women scores were better than homemakers. QOL in working women caregivers was better than homemakers' caregivers in social and environmental domains but statistically non-significant.

Key words: Quality of life index; Caregiver; World Health Organization-quality of life-BREF; Working women; Homemaker

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INTRODUCTION

In India, the role of the family has been vital in taking care of persons suffering from severe mental disorder. It includes supervising medications, arranging for follow-up, bringing the patient for inpatient care, staying with the patient, and providing financial support.[1]

According to a latest survey, every sixth Indian requires mental health help and it's more in 30–49 years of age group or above 60; among low-income strata and urban areas. The prevalence of psychiatric disorder according to gender has been found almost similar between lifetime. In male it is 1.5% and in females, it stands to be around 1.3%.[2,3]

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Care-giver is defined as any person including parents and other family members who with or without payment provides care, support, or assistance to a person with a disability.[3] Caregiver is a relative who stays with the patient, involved in looking after patient's daily needs, supervising medication, and accompanies him/her to the hospital.[4] All over the world, women are the predominant providers of informal care for family members with mental illness; and they may be working women or homemakers.[5] Working women earn the salary or wages through regular employment outside the home and easily juggle their career with raising children and taking care of various domestic chores.[6] Homemakers, besides managing the household chores also take care of the sick and elderly.[7] With the advancement of treatment modalities for the management of psychiatric patients, there is an increase in trend toward home-based treatment.[8] The tendency of caregiver is to get an early discharge of mentally ill patients even if they need hospitalization for acute illness and treat them at home.[9]

In India, women are twice more likely to become caregivers than men. Despite emergence of men as caregivers, researchers have not taken into account this trend and continue to maintain its traditional focus on female caregivers.[10] Yee and Schulz examined gender differences on caregiving had found women to spend more time on caregiving than men, which interfered with their work and social life to a greater extent.[11]

Stress is known as body reaction to any challenge and demand.[12] Hans Selye has described three stages that the body utilizes to react to any stressors called General Adaptation Syndrome (GAS). They are three stages of GAS: First Stage: Alarm stage which provides burst of energy. Second stage: Known as resistance stage the body utilizes to resist or adapt to the stresses. Third stage: Known as the exhaustion stage because energy is depleted.[13] There are external and internal factors for stress. External stress comes from outside: Our physical environment, relationship with others, job, etc., and internal stress comes from within, which determine our body's ability to respond and deal with stress.[14]

The quality of life (QOL) has been defined by World Health Organization (WHO) as an perception of an individual's about their position in life related to content of their value system and culture in which they live and its relation to their goals, expectations, standards, and concerns.[15] The QOL is better in working women as mostly working women don't abandon their caregiving responsibilities because of employment instead they cope to the best of their abilities with the combined pressures of caring for a loved one the toll that caregiving takes is not financial.[16]

Hence, the present study is aimed at assessing and comparing QOL among working women and homemaker women taking care of patients diagnosed with schizophrenia and bipolar affective disorder (BAPD).

Aims and Objectives

To assess and compare quality of life among working women and homemaker women taking care of patients diagnosed with schizophrenia and bipolar affective disorder.

MATERIALS AND METHODS

This was a hospital based, cross-sectional study. The caregivers were recruited from out-door patient department (OPD) of Psychiatry of Patna Medical College and Hospital, Patna according to the following criteria. This study was conducted from January 1, 2021 to June 31, 2021.

Inclusion criteria

1. Female participants who were either working or homemakers in the age group of 30–55 years and taking care of psychiatric patients diagnosed with Schizophrenia and BAPD of either sex brought to the psychiatry OPD
2. Caregiver (Mentally and physically healthy) who is a first-degree relative of the patient and staying with the patient at least for the past 2 years
3. Caregivers who give written informed valid consent.

Exclusion criteria

1. Caregivers with significant medical, neurological, and endocrinological disorders
2. Pregnant women
3. Caregivers with intellectual disability, mental illness, or substance use disorder.

Sample size estimation

Latest data from India reported moderate to severe levels of caregiver burden in 62% of the caregivers of psychiatric patients.[6] Taking the effect size of 10%, at 5% error and 80% power of the study, the estimated sample size is 135 using the formula:

$$n = (Z_{\alpha/2} + Z_{\beta}) \times PQ * 2/d^2,$$

were

n – Sample size

$Z_{\alpha/2}$ – Z value at 5% error (1.96)

P is the average prevalence of the character, Q is 1-P and d is the effect size.

So, by rounding off, we calculated the total sample size to be 140 and formed two groups. 70 caregivers were homemakers and 70 were working women.

Study design

Diagnosis of psychiatric illness was made as per ICD-10 criteria. A brief explanation about the study was given to the caregivers and informed consent was taken. The patients and caregivers identification data about socio-demographic status were recorded in Annexure-I and II. For assessment of caregivers' burden, their coping strategies in handling stress and impact on QOL subjects were administered "Caregiver Burden Questionnaire" (Annexure-III), "Coping Strategies Inventory" (Annexure-IV), and "WHO QoL–BREF" (Annexure-V). The study was conducted as per the good clinical practice guidelines and the declaration of Helsinki's Geneva with an approval of college ethical committee.

Instruments

1. Socio-Demographic Proforma (Annexure I and II): A Semi-structured proforma was used to obtain information about the participants and gather socio-demographic details including age, marital status, gender, educational status, economic status, history of substance use disorder, and any psychiatric illness
2. WHO QoL BREF: (Annexure V) The item scores range from 1 to 5. Because the numbers of items are different for each domain, the domain scores are calculated by multiplying the average of the scores of all the items in the domain by the same factor of 4. The domain scores would be having the same range starting from 4 to 20. Transformation of domain scores to a 0-to-100-point scale was made by using the WHO-QoL transformation table. The scale has been shown to have good discriminant validity, sound content validity and good test-retest reliability at several international WHO-QoL centers.[7]

RESULTS

Table 1 shows the comparison of socio-demographic data of Group 1 and Group 2 caregivers. No significant difference was found between the two groups when compared in relation to age group, relation and marital status.

Table 2 shows the diagnostic classification of the psychiatric illness of patients in both the groups as per ICD 10. F20 (Schizophrenia) and F31 (BAPD) was reported among 40%, 60% and 41.43%, 58.57% of the subjects among Group 1 and Group 2, respectively. Overall, the study comprised of 57 Schizophrenic patients (40.71%) and 83 (59.29%) BAPD patients. The difference between the groups was statistically non-significant at P>0.05.

Table 3, shows the total time spent by the caregiver on psychiatry patient amongst groups. 1–8, 9–14, >14–19 and >19–24 h were spent by 25.71%, 57.14%, 12.86%, 4.29% and 60%, 38.57%, 1.43%, 0% of the caregivers in Group 1 and Group 2, respectively. In conclusion, most of the caregivers in group 1 (57.14%) spent 9–14 h whereas caregivers in group spent 1–8 h (60%) with statistically significant differences (χ^2=6.98, P=0.02).

Table 4 shows the WHO-QOL comparison among Group 1 and Group 2. Mean physical, psychological, social and environmental was 12.42, 11.60, 12.24, 12.62 and 14.46, 13.28, 11.28, 12.28 of the caregivers in Group 1 and Group 2, respectively. When mean physical (χ^2=4.11, P=0.03), psychological (χ^2=3.42, P=0.04) was compared among the two groups, the difference was found to be statistically significant as P<0.05. QOL in Group 2 caregivers (Working Women) is better than Group 1 caregivers (Homemakers) in physical and psychological domains.

However, QOL in Group 1 caregivers (Homemakers) is better than Group 2 caregivers (Working Women) in social and environmental domains but statistically non-significant.

DISCUSSION

The present study was a hospital based, cross-sectional study. The total of n=140 caregivers were enrolled. They were further divided into two groups, Group 1 (Homemaker women) and Group 2 (Working women) of 70 caregivers each and were in the age group of 30–55 years. People with mental illness (PMI) comprised of both schizophrenia and BAPD who reported to Psychiatry OPD of Government Medical College and Rajindra Hospital, Patiala accompanied by their caregivers.

In the present study, approximately 55% of the caregivers were mothers of PMI while 31% were wives. Aggarwal et al.,[17] also reported similar findings. who reported majority of the caregivers to be married 76% but only 36% of PMI were taken care by their spouses. A study by Mohammed and Ghaith (2018)[18] revealed that more than two-fifths of caregivers were parents, less than one-third were son and daughter, one-fourth were spouses and only 4% of them were siblings. The higher percentages of caregivers being parents can be explained due to fact that an early onset of mental illness, which hinders with the patient prospects of an early marriage. So, parents become the natural caregivers who bring their children for treatment. The Indian societal values are such that if a person becomes mentally ill, spouses might leave him, but parents rarely abandon their children.

Table 1: Sociodemographic data of caregivers among Group 1 (Home-maker women) and Group 2 (Working women)

Age of caregivers (in years)	Group 1 (Homemakers)		Group 2 (Working Women)		Chi-square	P-value
	n=70	%	n=70	%		
30–35	14	20.00	15	21.43	1.78	0.21
31–40	8	11.43	11	15.71		
41–50	12	17.14	24	34.29		
51–55	36	51.43	20	28.57		
Relationship of caregiver with Patient						
Bhabhi	3	4.29	4	5.71	1.46	0.28
Grandmother	4	5.71	6	8.57		
Mother	41	58.57	38	54.29		
Wife	22	31.43	22	31.43		
Marital status						
Single	0	0	0	0	0.89	0.67
Married	70	100	61	87.14		
Remarried	0	0	0	0.00		
Widowed	0	0	8	11.43		
Divorced	0	0	0	0.00		
Separated	0	0	1	1.43		

Table 2: Diagnostic classification of psychiatric illnesses of patients in both the groups as per ICD-10

ICD 10 Diagnosis of Patients	Group 1 (Homemakers)		Group 2 (Working Women)		Total (%)	Chi-square	P-value
	n=70	%	n=70	%			
F20 (Schizophrenia)	28	40	29	41.43	57 (40.71)	0.11	0.82
F31 (BAPD)	42	60	41	58.57	83 (59.29)		

BAPD: Bipolar affective disorder

Table 3: Total time spent in caregiving by caregiver in Group 1 and Group 2

Caregivers Time Spent (in hours)	Group 1 (Homemakers)		Group 2 (Working Women)		Chi-square	P-value
	n=70	%	n=70	%		
1–8	18	25.71	42	60	6.98	0.02*
9–14	40	57.14	27	38.57		
>14–19	9	12.86	1	1.43		
>19–24	3	4.29	0	0		

P<0.05: Significant (*)

Table 4: Comparison of quality-of-life index on WHO-QoL-BREF scale in Group1 and Group 2

Caregivers WHO-QOL	Group 1 (Homemakers)		Group 2 (Working Women)		t-test	P-value
	Mean	SD	Mean	SD		
Q1	11.27	2.08	11.86	2.51	1.72	0.14
Q2	11.68	2.43	11.93	2.58	1.28	0.32
Physical	12.42	2.57	14.46	3.69	4.11	0.03*
Psychological	11.60	2.40	13.28	3.25	3.42	0.04*
Social	12.24	3.22	11.28	3.25	2.36	0.09
Environmental	12.62	2.40	12.28	3.25	1.02	0.49

P<0.05: Significant (*)

Present study also revealed that 57.14% (n=40) caregivers in Group 1 spent 9-14 hours per day in care giving. However, in Group 2, 60% spent 1-8 hours per day in caregiving. The difference in time spent in caregiving role was statistically significant among the groups. The same study founded that the amount of caring hours for patients were more than 12 hours per day for 55% of the caregivers. 58% of them were not providing care for other members of the family. 51% of the caregivers were having other persons who were helping them in caring their mentally ill patients. This high time requirement may be because of the chronic nature and severity of symptoms that characterize mental illness, which require constant care and supervision.

In today's scenario, the husband and wife both work together to create a balance between their work life as well as at home but still it is very difficult for working women to play multiple roles of a cook, mother, wife, a nurse as well as cater to the demands of office work. So, working women can't be able to spend much time on caregiving as she has to fulfill the demands both at work and home or caregiving.

In present study, mean score physical, psychological, social and environmental quality of life domain was 12.42, 11.60, 12.24, 12.62 and 14.46, 13.28, 11.28, 12.28 of the caregivers in Group 1 (Homemakers) and Group 2 (Working women), respectively with statistically significant difference in the present study. So, it was observed that physical and psychological domain of QoL of Group 2 is better than Group 1. In a study by Basheer et al., (2005),[19] the mean score was 15.15 in the physical domain, 12.75 in social, 12.96 in environmental and 12.52 in the psychological domain. Neong et al., (2018)[20] revealed similar results as they found that the highest mean scores for the respondents were in the physical domain, followed by social, psychological domain and environmental domain.

The Physical domain showed that our study population had good activities of daily living, energy level and mobility, less discomfort, optimal sleep and rest, and good capacity to work. The less psychological domain score in our study showed negative attitude in life and decreased self-esteem. This can be due to the social stigma associated with the mental illnesses. Our results was congruent to a previous study conducted in Taiwan.[21]

The negative effect of care on the caregivers' quality of life accompanies other side effects such as poor mental health, additional use of anti-depressants and increased requirement of medical and hospital care (Ayalew et al).[22] Mital et al concluded that as families spend their time on caring their patients, no time is left for them to enjoy life and have recreation. frustration, stress, fear, lack of support and constant doubt were some complaints the mental patients' families stated in their quality-of-life evaluation.[23]

Limitations of the study

- The study is limited by the small sample size and its cross-sectional design
- The caregivers were screened for the presence of a psychiatric disorder using a clinical interview and a formal assessment was not carried out
- The psychological distress experienced by caregivers may have influenced their ratings of burden.

CONCLUSION

In physical and psychological domain of QOL, working scores were better than homemakers. QOL in working women caregivers was better than homemakers caregivers in social and environmental domains but statistically non-significant.

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ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Radiological study of Os trigonum and its clinical significance

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ABSTRACT

Background: Os trigonum (OST) is commonly located on the posterior aspect of the talus. It occurs as a result of secondary ossification center failing to fuse with the lateral tubercle of the posterior process of the talus; its incidence varies between 2 and 25%, and is more often bilateral. It occurs as an intra-articular Os, which is most often securely rooted to the lateral tubercle of the talus by a fibrocartilaginous synchondrosis. **Aims and Objective:** To determine the incidence, morphology, and distribution of Os Trigonum (OST). **Materials and Methods:** Retrospective 500 lateral foot radiographs view were studied to determine the incidence, morphology, and distribution of OST. **Results:** Incidence of OST in the present study was 6.6%, with predominantly round or ovoid in shape. OST was located on the posterolateral aspect of the talus. **Conclusion:** OST can be one of the causative factor responsible for Flexor hallucis longus tendonitis, OST syndrome, which occur in plantarflexion of the ankle, leading to compression of the OST between the distal tibia and the calcaneus. Hence, knowledge regarding the incidence, morphology, and distribution of OST is important for the radiologist, orthopedic surgeons to arrive at a correct diagnosis, which aids in the management of cases presenting with complaints of posterior ankle pain.

Key words: Os trigonum; Os trigonum syndrome; Posterior ankle pain; Flexor hallucis longus tendonitis

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INTRODUCTION

Os trigonum (OST) is a foot ossicles which occurs due to failure of fusion of ossification center or development of additional center which is incidentally identified in routine radiographs. It is one of the normal variant found on the posterior aspect of talus; its incidence varies from 2 to 25% in the earlier studies.[1-5] It can be triangular, round, or oval in shape, more often bilateral usually single in number but can be bipartite or multi partite and is best visualized on lateral foot radiographs. It is usually <1 cm in size. Margins of OST are either smooth or serrated in appearance.[4,6] When triangular it presents with three surfaces anterior, inferior, and posterior. The anterior surface articulate with the lateral tubercle of talus by fibrocartilaginous synchondrosis, while the inferior surface articulate with calcaneum and the posterior surface forms non-articular area and provides attachment to posterior talocalcaneal and posterior talofibular ligaments one must be familiar with such normal anatomical variants in order to prevent their misinterpretation and overtreatment in cases of trauma and ankle sprain.[4]

Ankle impingement is one of the causes of subacute to chronic ankle pain. In hyper plantar flexion OST can impinge on the posterior border of tibia which is more commonly seen in ballet dancers, athletes, and soccer players. OST syndrome or posterior ankle impingement (PAI) results from blunt foot trauma and is usually associated with pain and tenderness at the ankle joint.[4-7]

Knowledge regarding OST is important to identify the potential cause of posterior ankle pain and to decide on the conservative or surgical line of management. Hence, a radiographic study on OST was done to determine the incidence, morphology, and distribution of OST in the

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foot radiographs and has been reported for its clinical significance.

Aims and objectives

To determine the incidence, morphology, and distribution of OST.

MATERIALS AND METHODS

Consecutive 500 normal lateral foot radiographs of both sexes were selected using a convenient sampling method and incorporated in the study to determine the incidence, morphology, and distribution of OST. Descriptive analysis was applied and results were expressed in the form of average and percentage. The study was preapproved by the Institutional Ethics Committee for the final permission.

Inclusion criteria

All subjects belonging to any gender with age ranging from 12 to 80 years.

Exclusion criteria

Radiographs with incorrect patient positioning, foot deformity, fractures of metatarsal and tarsal bones were excluded from the study.

RESULTS

Out of 500 radiographs of the foot, 33 cases of OST were observed with varying shape and size, which accounts for 6.6 % the incidence (Table 1). Shape of OST was predominantly round (Figure 1) or oval (Figure 2); being separated from the talus by a radiolucent line, with a well-corticated appearance and distinct margins. It was located posterolateral to the talus bone. Incidence of OST was more in males (8.27%) compared to females (4.7%) (Table 2).

DISCUSSION

Accessory ossicles of the foot are commonly confused for avulsion fractures of the foot, leading to misdiagnosis and overtreatment in cases of trauma.[1,5,6] OST was first described in 1804 by Rosenmuller.[2,7] OST is an accessory ossicle located posterolateral to talus; it has an incidence ranging from 2 to 25%.[1-5] Incidence of OST was 6.6% (Table 1) among the study population, however Uygur et al.,[1] reported in his study an incidence of 15.4%, which is comparatively higher than present study.

OST can be triangular, oval, or round in shape, they are best visualized on lateral radiographs,[2,4] however, in the present study it was predominantly oval or round in shape. Incidence of OST was more in males 8.27% (22 males) compared to females 4.7% (11 females) (Table 2) which correlates with an earlier study by Uygur et al.,[1] who has also reported a higher incidence in males (55.3%) compared to females (44.6%).[1]

PAI syndrome/OST syndrome can be caused due to various factors such as Stieda process fracture, an avulsion injury of the posterior talofibular ligament, or cartilaginous synchondrosis disruption, Flexor hallucis longus (FHL) tendonitis. It frequently occurs bilateral being common

Table 1: Incidence of Os trigonum

	No. of radiographs with Os trigonum	Absence of Os trigonum	Total
Incidence of Os trigonum	33	467	500
Percentage of Os trigonum	6.6	93.4	100

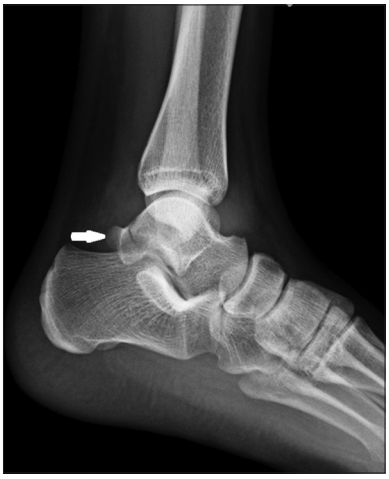

Figure 1: Lateral radiograph of the foot of 52 years male, arrow depicting a small rounded OST located posterolateral to the talus

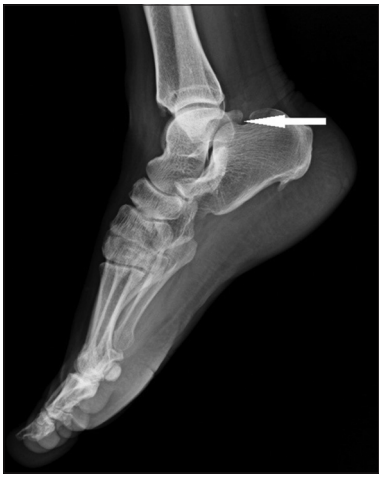

Figure 2: Lateral Radiograph of the foot of 40 years male, arrow indicating an oval-shaped OST

Table 2: Os trigonum incidence in male and female subjects

	No. of radiographs with Os trigonum (%)	Absence of Os trigonum (%)	Total
Male (266)	22 (8.27)	244 (91.72)	266
Female (234)	11 (4.7)	223 (95.29)	234
Total	33 (6.6)	467 (93.4)	500

in soccer players, runners, and gymnasts, due to repeated plantar flexion of the ankle.[6,8-12] It is predominantly symptomatic in men compared to women.[3] Repetitive dorsiflexion of the foots, metatarsophalangeal joint, and plantarflexion of the ankle, can result in FHL tendonitis, tenosynovitis.[9,12]

OST resulting from failed fusion of secondary ossification center of lateral tubercle of the talus can be differentiated from avulsion fractures of the talus, by remarkably sharp edges and discontinuity of the cortical lining. Hyper plantarflexion of the ankle may result in posterior ankle fractures, which are commonly misdiagnosed and treated as simple ankle sprains, which can present with nutcracker sign. Painful OST syndrome should be considered as one of the differential diagnosis in patients presenting with recalcitrant posterolateral ankle pain.[6,8]

Painful OST can be effectively managed by conservative methods and appropriate physical therapy. Fractures of OST is very rare and can be efficiently treated with rest, ice packing, anti-inflammatory drugs, bracing, stretching, and strengthening exercises of the ankle and foot, in order to provide symptomatic relief, while increasing the range of movement and strength. If conservative treatment fails, excision of OST is indicated in symptomatic patients.[6,8]

OST is considered as a secondary ossification center which has failed to fuse with the posterior aspect of the talus.[7] Being an intraarticular os it is connected to the lateral tubercle of the talus by fibrocartilaginous synchondrosis.[6] Ossification center for OST appears between 8 and 13 years and usually fuses with the talus within 1 year with talus to form trigonal (Stieda) process. However, in 7–14% of individuals, OST persists, which is very difficult to differentiate from avulsion fracture of the talus.[4,13] Hence, OST must be borne in mind in treating patients with posterolateral ankle pain.

Limitations of the study

Although radiology being the initial mode of investigation, Ultrasonography, and MRI, can give a much clear view of the OST along with adjoining soft tissue mass and aid in the early diagnosis and management of posterior ankle pain.

CONCLUSION

Radiologists and surgeons must be aware of the ossicles of the foot such as OST so as to prevent their interpretation as fractures of tarsal bones or visa versa. OST is commonly misdiagnosed as peroneal tendinitis, avulsion fracture of talus in dancers presenting with posterolateral ankle pain. Hence, knowledge pertaining to the incidence, location, and morphology of OST can help in preventing misdiagnosis, it also aids in the early diagnosis of cases presenting with posterolateral ankle pain. By recognizing and treating this in symptomatic cases; progressive, debilitating deformity either conservatively or surgically, the surgeons will be able to resolve discomfort, improve joint function, and restore the quality of life of the patient.

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CASE REPORT ASIAN JOURNAL OF MEDICAL SCIENCES

High-grade mucoepidermoid carcinoma in thyroglossal cyst: Post-surgical histological surprise and dilemmas

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ABSTRACT

Occurrence of malignancy in the TG cyst has been rarely reported, though rare, and papillary carcinoma predominates the common type but squamous cell carcinomas, anaplastic carcinoma, and medullary have been reported rarely. Mucoepidermoid carcinomas are most commonly seen in salivary glands, and as per the available literature, there was only two cases reported in thyroglossal cyst. We are presenting a 67-year-old lady presented with a 6×8 cm hard swelling below symphysis menti with no thyromegaly and moving on protrusion of tongue, and on MRI, it was found to be thyroglossal cyst with infiltration of strap muscles. Cytological investigation revealed it to be a TG cyst malignancy. The patient underwent total thyroidectomy and radical Sistrunk's operation. Histopathological and immunohistochemistry revealed it to be a histological examination revealed a low-grade mucoepidermoid carcinoma consistent with origin in a thyroglossal duct remnant it invaded the hyoid bone and adjacent strap muscles. Various diagnostic and treatment dilemmas in the treatment of TG cyst malignancy are discussed with reference to mucoepidermoid carcinoma. We are reporting an usual histological surprise in a thyroglossal cyst malignancy being the only second reported case of TG cyst mucoepidermoid carcinoma this case highlights the importance of removal of thyroglossal duct cysts at an early stage and aggressive surgical approach in high-grade tumors.

Key words: TG cyst; Mucoepidermoid carcinoma; Sistrunk's operation; High grade

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INTRODUCTION

Thyroglossal cyst is the most common congenital abnormality of thyroid gland development affecting pediatric age group but also in older age group.[1] Thyroglossal cyst can have ectopic thyroid tissue varied from 1.5% to 45% of cases.[2]

Occurrence of malignancy in the cyst has been rarely reported, though rare and till date, 278 cases are reported in the literature[3] and papillary carcinoma predominates the common type but squamous cell carcinomas, anaplastic carcinoma, and medullary have been reported rarely.

Mucoepidermoid carcinomas are most commonly seen in salivary glands, however, it is also reported from glandular tissue of lung, lacrimal glands, and thyroid. There are around 42 cases of mucoepidermoid carcinomas from world literature and mostly they are low grade. We are reporting the second reported case of mucoepidermoid carcinoma in thyroglossal cyst with local infiltration. There are diagnostic and management dilemmas in this condition and consensus is yet to be reached.

We are presenting a 67-year-old lady presented with a 6 × 8 cm hard swelling below symphysis menti with no thyromegaly and moving on protrusion of tongue, and on MRI, it was found to be thyroglossal cyst with infiltration

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of strap muscles. Cytological investigation revealed it to be a TG cyst malignancy. The treatment plan and histopathological surprise that followed is discussed in detail.

PRESENTATION OF THE CASE

A 67-year-old lady presented to general surgery OPD, with complaints of a swelling below chin in the upper neck which she noticed 5 months back. Swelling was painless, moving with deglutition and rapidly progressed in size. There was associated discomfort while swallowing. She was known hypertensive on antihypertensives. Clinical examination revealed that there was a 6 × 8 cm sized oval hard non-tender swelling in submental region in midline extending from 2 cm below symphysis menti to just above the level of hyoid bone, and 3 cm to the midline on either side. It was moving with deglutition and with the protrusion of tongue. Thyroid gland was not enlarged. NO palpable cervical lymphnodes. Oral cavity examination was normal.

Ultrasound neck reported as heterogeneous lesion with necrotic collection in submental region in midline measuring 2.5 × 2 × 2 cm with bilateral sub-centimetric level 3 and 4 lymph nodes.

MRI scan was taken which showed an ill-defined heterogeneously enhancing soft-tissue lesion 39 × 37 × 24 mm in midline in submental pre-hyoid region extending to anterior surface of thyroid cartilage (Figure 1) which appears to be embedded in the left strap muscles. Few intralesional cystic areas noted. Lesion was found to be extending posteriorly in pre epiglottic region. Mild bone marrow edema of hyoid bone and thyroid cartilage noted, findings were suggestive of thyroglossal duct cyst lesion with possible malignant infiltration. Thyroid gland visualized normally with no focal lesions.

Fine-needle cytology showed cells suggestive of papillary carcinoma. The patient was prepared was operated. On exploration there a 4 × 5 cm hard lesion above the Hyoid This lesion was found to be infiltrating right strap muscles and body of hyoid. Thyroid appeared to be normal morphology. We proceeded with Sistrunk operation along with total thyroidectomy and Level VI central nodal dissection [Figure 2].

Histological examination revealed a low-grade mucoepidermoid carcinoma consistent with origin in a thyroglossal duct remnant. It invaded the hyoid bone and adjacent strap muscles [Figure 3].

DISCUSSION

Carcinoma arising in a TGDC is a very rare and accounts for less than 1%.[4] Approximately 280 cases of malignant tumors in thyroglossal cyst are reported up to 2020 and rarely thereafter. Most common histological type is papillary carcinoma (80–95%) followed by mixed papillary-follicular carcinoma (8%) and squamous cell carcinoma (6%).[5] It also has to be noted that other cancers such as follicular, squamous cell carcinoma, and Hurtle cell carcinoma are described rarely in the literature.[6] Very rarely there are

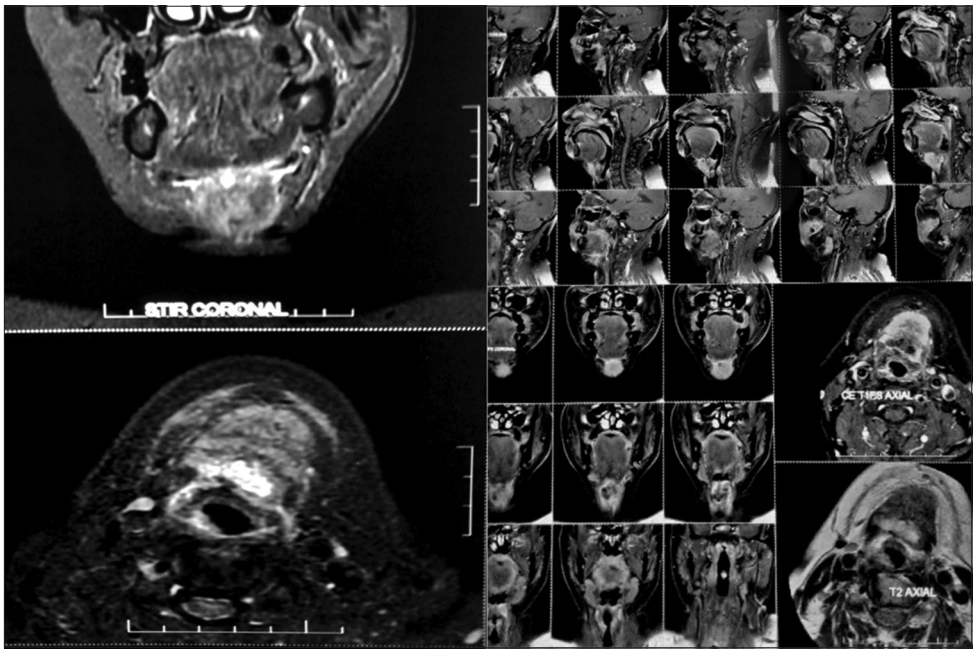

Figure 1: MRI shows an ill-defined heterogeneously enhancing soft-tissue lesion 39 × 37 × 24 mm in midline in submental pre-hyoid region extending to anterior surface of thyroid cartilage which appears to be embedded in the left strap muscles.

reported cases of anaplastic carcinoma and one reported case of mucoepidermoid carcinoma. It is very important to emphasize that genetic positivity of TITF1, TITF2, and PAX8 and the gene for the thyroid-stimulating hormone receptor.

The knowledge about the thyroid mucoepidermoid carcinoma is still evolving and it is shown that these low-grade tumors are shown to be positive for the t(11;19)(q21;p13) translocation[7-10] but the lack of this translocation in high-grade tumors points to the fact that these tumors are biologically and molecularly different entity. The histogenesis of thyroid or thyroglossal cyst MEC is explained by two theories that it develops from solid cell nests (SCNs) or thyroid follicular epithelial cells.[11]

These SCNs are multipotent cells which have been linked to several thyroid cancers, including papillary and MEC. Alternatively, it is thought that papillary carcinoma (the most common malignancy found in thyroglossal duct remnants) may undergo squamous and mucinous metaplasia resulting in MEC.[12,13] However, it is still unclear that MEC in a thyroglossal duct remnant has arisen through the same means as a thyroid MEC or through another as yet unspecified mechanism.

Even though the treatment of thyroglossal duct carcinoma is still evolving , consensus have been attained in most areas. Conservative management with Sistrunk procedure alone is recommended for papillary thyroid cancer in low-risk patients who are female and younger than 40 years old, with no invasion of the capsule and a low-grade tumor of less than 1 cm in size.

In the case of large tumors >1 cm, invasion through the duct cyst wall, or suspect foci in the thyroid gland, a total thyroidectomy followed by I131 ablation and thyroid-stimulating hormone suppression is the most frequently proposed treatment.[14] In pure squamous cell carcinomas of TG cyst, the Sistrunk procedure is the only warranted procedure.

Regarding MEC, the low-grade tumors can be treated by Cistrunk's operation but aggressive treatment is warranted in high-grade tumors and the available literature supports the use of adjuvant radiotherapy in cases of high-grade tumors, which generally carry a poor prognosis.[15] The use of radioiodine ablation due to the possible origins of these tumors having dedifferentiated from other thyroid neoplasms has been advocated by some authors.[16]

Regarding cervical lymph nodes, even if these are not palpable, clinically frozen sections are considered to be

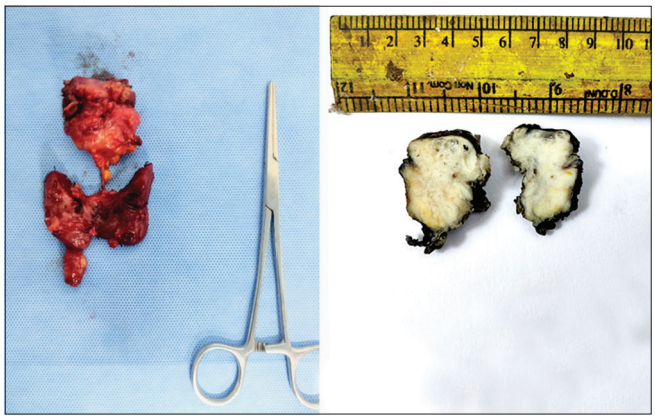

Figure 2: Macroscopic specimen from total thyroidectomy and Sistrunk operation: A single nodular mass measuring 4.5 × 3.2 × 3 cm, with attached hyoid bone. Cut surface demonstrates ill-defined tumor mass with interspersed cysts

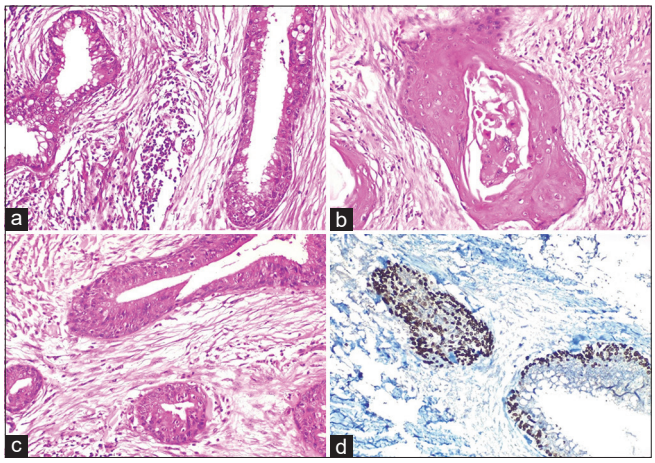

Figure 3: Microscopic histopathology demonstrating (a) mucus secreting cells, (b) intermediate cells, and (c) epidermoid cells in the high-power view. (d) p63 immunohistochemistry confirms epidermoid differentiation

mandatory. Radical or modified radical neck dissection is indicated only in the presence of positive lymph nodes.[17] As the frequency of nodal metastasis is relatively small the survival is 95.5% at 10 years.

CONCLUSION

We are reporting an usual histological surprise in a thyroglossal cyst malignancy being the only second reported case of TG cyst mucoepidermoid. This case highlights the importance of removal of thyroglossal duct cysts at an early stage and aggressive surgical approach in high-grade tumors.

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