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Effects of intravenous clonidine on hemodynamics and plasma cortisol level during laparoscopic urological surgeries in a tertiary care hospital

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ABSTRACT

Background: Laparoscopic urologic surgeries causes rise in Blood pressure and heart rate. Maintenance of hemodynamics is an essential part of anaesthetic management. **Aims and Objectives:** The aim of the study was to observe the effects of intravenous clonidine on heart rate (HR) and mean arterial pressure (MAP) and plasma cortisol level during laparoscopic surgeries. **Materials and Methods:** In this ethical committee approved double-blind prospective interventional study, 50 adult patients of both sexes with ASA I and II were randomly allocated to two groups: Group C (3 mcg/kg Clonidine in 20 ml of Normal saline) and Group P (20 ml Normal saline). HR and MAP were recorded at different time intervals and blood samples were drawn before induction and after reversal from general anesthesia. **Results:** In Group P there was a significant increase in variables during intubation, pneumoperitoneum and release of gas from the abdomen ($P<0.001$). In Group C mean plasma cortisol level increased from 19.36 ± 1.49 (before induction) to 28.60 ± 1.21 (after reversal) and in Group P from 19.33 ± 1.30 to 32.28 ± 1.66. **Conclusion:** Clonidine may be a suitable and safe medication to attenuate hemodynamic stress response during laparoscopic surgeries.

Key words: Clonidine; Cortisol; Laparoscopy; Pneumoperitoneum; Stress response; Urosurgery

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INTRODUCTION

Minimal access surgery and laparoscopic surgery have seen a marked improvement in the last few decades. Performance of the first laparoscopic procedure was attributed to George Kelling and the procedure was called celioscopy.[1,2] Although laparoscopy involves minimal invasion and tissue damage, it has potentially serious complications, including cardiopulmonary effects that result mainly from hypercarbia and raised intra-abdominal pressure caused by pneumoperitoneum.[3] Hypercapnia activates the sympathetic nervous system leading to an increase in blood pressure, heart rate (HR), and systemic vascular resistance. General anesthesia and controlled ventilation comprise the accepted anesthetic technique to reduce the increase in $PaCO_2$.[4] Various pharmacological agents such as nitroglycerine, beta blocker, and opioids are used to provide hemodynamic stability during pneumoperitoneum. The short-term benefits of minimal access techniques include less pain, early mobilization, and shorter hospital stay.[5,6]

Regarding laparoscopic urological surgeries, the emphasis is on the principles of enhanced recovery, the pre-operative risk assessments, as well as the specific management plans to reduce the incidence of complications arising as a result of the prolonged pneumoperitoneum and steep head down

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positions.[7,8] The present study was undertaken with the objective of evaluating any beneficial effect of intravenous clonidine on hemodynamics and plasma cortisol level during laparoscopic urological procedures.

Aims and objective

The objective of the study was to find the effects of intravenous clonidine on hemodynamics and plasma cortisol level during laparoscopic urological surgeries in a tertiary care hospital.

Specific objective

The specific objectives are as follows:

1. To study the effect of intravenous clonidine on HR and blood pressure during laparoscopic surgeries
2. To study the effect of intravenous clonidine on the release of cortisol and other adrenocorticotrophic hormones during laparoscopic urological surgeries
3. Side effects of clonidine, if any.

MATERIALS AND METHODS

This prospective randomized double-blind interventional study was conducted at Urology OT of a tertiary Hospital between January 2020 and June 2021.

After taking approval from institutional ethics committee (IPGMER/IEC/2020/292) and obtaining CTRI registration (CTRI/2021/03/032354.), 50 consenting patients of ASA physical status I, II of either sex and between the age group of 18 and 60 years scheduled for laparoscopic urological surgery were included in the study.

Sample size for this study was calculated on the basis of mean arterial pressure (MAP) as the primary outcome measure. It was calculated that 21 subjects should be required per group in order to detect a difference of 10 mm Hg in MAP at 1 min after intubation or 5 min after pneumoperitoneum with 90% power and 5% probability of type 1 error. This calculation assumed SD of 10 mm Hg for MAP and two sided testing. Rounding off, the recruitment target was being kept at 25 subjects per group. Sample size calculation was done by nMaster/software 2.0 (Department of Biostatistics, Christian Medical College, Vellore; 2011).

Patients were randomized using sealed envelope technique into

- Group C-received IV Clonidine 3 mcg/kg in 20 ml normal saline
- Group P - received IV 20 ml normal saline only.[9]

Patient as well as primary investigator was unaware of the group allocation, group allocation and blinding technique shown in consort diagram (Figure 1).

Thus inclusion criteria of this study were consenting patients undergoing laparoscopic nephrectomy, nephroureterectomy, pyeloplasty, and vesicovaginal fistula.

Patients who did not give consent for the study, patients undergoing laparoscopic adrenalectomy, patients with chronic obstructive pulmonary disease, uncontrolled hypertension and diabetes mellitus, severe coronary insufficiency, and recent myocardial infarction were excluded from the study. Procedures were conducted in accordance with the Helsinki Declaration-2013.

Preanaesthetic check-up was conducted a few days before surgery. Patients were evaluated for any systemic diseases, laboratory investigations were checked and recorded. The procedure of general anesthesia was explained to the patients in a language they understand and consent was taken.

The patients were allowed to take solid food at 10:00 pm and received tablet Pantoprazole 40 mg and tablet Alprazolam 0.5 mg orally as premedication at night before surgery. They were allowed to take plain water up to 6 am.

Patients were randomly divided into two groups of 25 each - Group C and Group P at the preoperative waiting room. After that pulse oxymeter and NIBP were attached and IV cannulation was done and Ringer Lactate infusion started. IV glycopyrrolate 0.2 mg and IV ondansetron 50 mcg/kg IV were given half an hour before induction. Baseline HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, and oxygen saturation (SpO_2) were measured 10 min after giving premedication.

After that Group C was started with Clonidine infusion at 3 mcg/kg in 20 ml normal saline 10 min before induction and Group P was started with infusion normal saline in 20 ml syringe at the same rate and before 10 min. Any incidence of bradycardia (HR <50) was treated with IV atropine 0.6 mg. After completion of drug infusion HR, MAP was recorded at 1, 5, and 20 min.

After that patients were shifted to OT, patients were attached with standard ASA monitors and induced with Propofol 2–3 mg/kg, IV fentanyl 2 mcg/kg, and IV succinylcholine 1.5–2 mg/kg body weight. Patients were intubated with appropriate size cuffed endotracheal tube. After intubation HR, MAP was recorded at 1, 3, and 5 min. Anesthesia was maintained with 67% nitrous oxide and 33% oxygen and isoflurane 0.4%. Muscle relaxation was maintained with IV atracurium 0.3 mg/kg loading dose with top ups of 0.1 mg/kg. HR and MAP were recorded 15 and 30 min after pneumoperitoneum and 10 and 15 min after release of CO_2 from the abdomen.

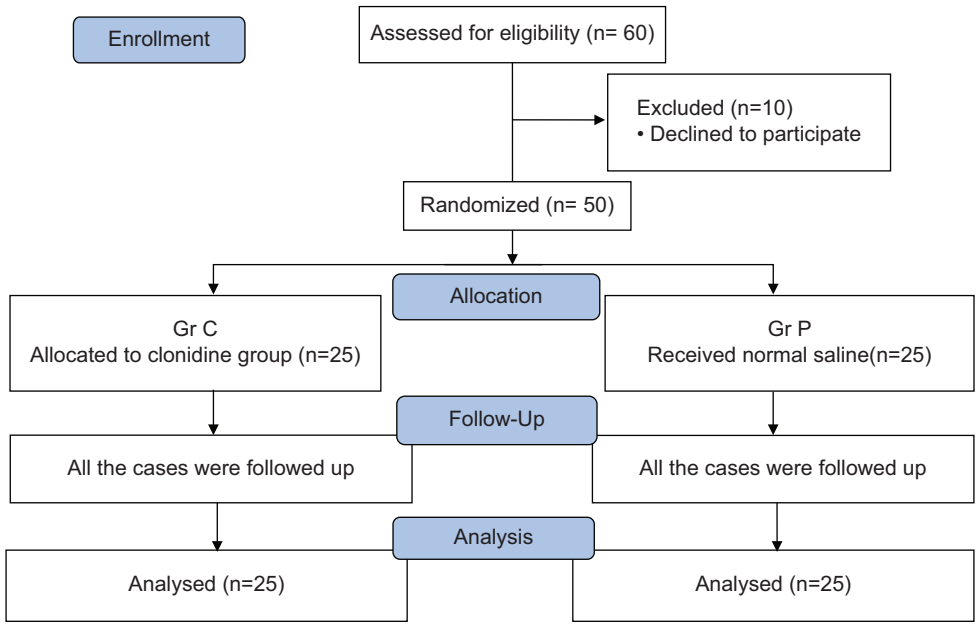

Figure 1: Consort flow diagram

After surgery, reversal was achieved with IV neostigmine 0.05 mg/kg and IV glycopyrrolate 0.01 mg/kg.

Blood samples were drawn before induction of general anesthesia and after reversal from general anesthesia for plasma cortisol levels.

After adequate recovery, patients were shifted to post anesthesia care unit and monitored for 6 h and later shifted to ward.

RESULTS

Statistical analysis was carried out in this present study by Statistical Package for the Social Sciences (SPSS V.24 SOFTWARE.) Hemodynamic variables were represented by mean±SD. Statistical significance in mean difference was done using analysis of variance, student t' and Chi-square tests as appropriate. P≤0.05 was considered as statistically significant.

Table 1 shows the demographic profile of two groups.

Table 2 and Figure 2 shows distribution of age in between the two groups (values are in percentage with 95% CI)

Table 3 and Figure 3 shows distribution of gender between the two groups (values are in percentage with 95% CI)

Table 4 and Figure 4 shows distribution of participants in terms of ASA (values are in percentage with 95% CI)

Table 1: Summary of basic details

Basic Details	Mean±SD||Median (IQR)||Min-Max||Frequency (%)
Group	
C	25 (50.0)
P	25 (50.0)
Age (Years)	36.58±9.37||36.50 (30.00–42.00)||18.00–56.00
Age	
18–30 Years	14 (28.0)
31–40 Years	19 (38.0)
41–50 Years	13 (26.0)
51–60 Years	4 (8.0)
Gender	
Male	27 (54.0)
Female	23 (46.0)
ASA	
I	22 (44.0)
II	28 (56.0)
Type of surgery	
Nephrectomy	20 (40.0)
Pyeloplasty	15 (30.0
Urethroplasty	14 (28.0)
Vesicovaginal Fistula Repair	1 (2.0)

Table 2: Distribution of the participants in terms of age (n=50)

Age	Frequency	Percentage	95% CI
18–30 Years	14	28.0	16.7–42.7
31–40 Years	19	38.0	25.0–52.8
41–50 Years	13	26.0	15.1–40.6
51–60 Years	4	8.0	2.6–20.1

Table 5 and Figure 5 show distribution of participants in terms of different surgery (values are in percentage with 95% CI)

Table 6 and Figure 6 show comparison of MAP over time between groups (values are in mean±SD)

Table 7a and Figure 7 show comparison of change in MAP from baseline to different tie intervals between groups (values are in mean±SD)

Table 7b and Figure 8 show comparison of change in MAP from baseline to different intervals between groups (values are in mean±SD)

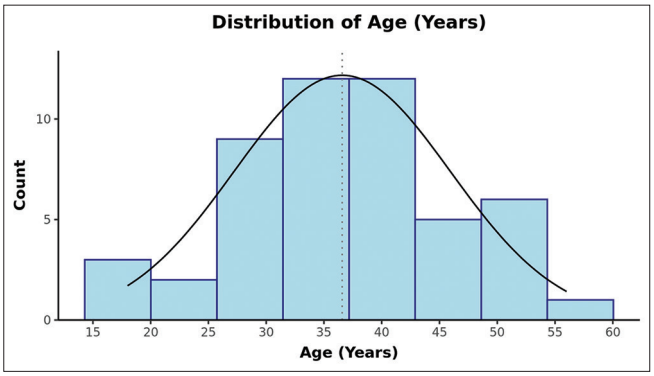

Figure 2: The distribution of age in years. The variable age (Years) was normally distributed (Shapiro–Wilk Test: P=0.622). The mean±SD of Age (Years) was 36.58±9.37

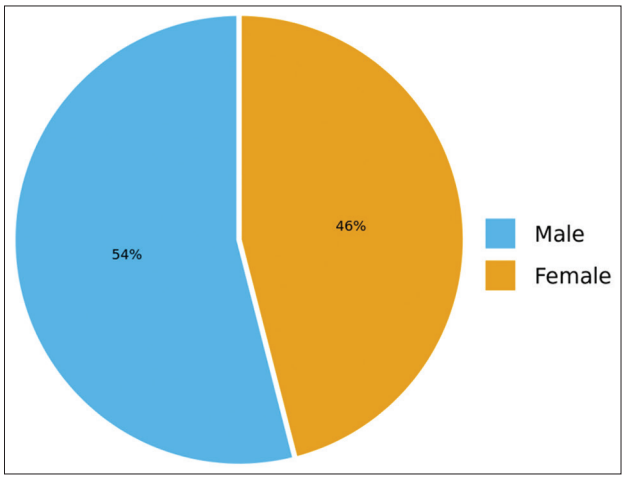

Figure 3: The pie diagram of distribution of gender

Table 3: Distribution of the participants in terms of gender (n=50)

Gender	Frequency	Percentage	95% CI
Male	27	54.0	39.5–67.9
Female	23	46.0	32.1–60.5

Table 4: Distribution of the participants in terms of ASA (n=50)

ASA	Frequency	Percentage	95% CI
I	22	44.0	30.3–58.7
II	28	56.0	41.3–69.7

Table 8 and Figure 9 show comparison of HR over time between groups (values are in mean±SD)

Table 9a and Figure 10 show comparison of change in HR from baseline to different intervals between groups (values are in mean±SD)

Table 9b and Figure 11 show comparison of changes in HR from baseline to different intervals between groups (values are in mean±SD)

Table 10 and Figure 12 show changes in plasma cortisol level between the groups (values are in mean±SD.

Table 1 shows the demographic profile across the group.

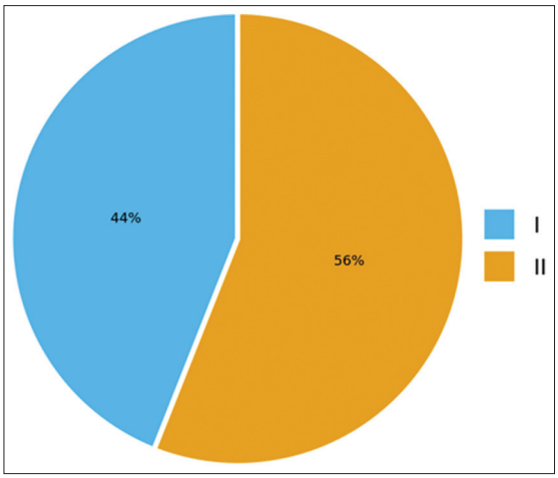

Figure 4: The pie diagram of distribution of ASA

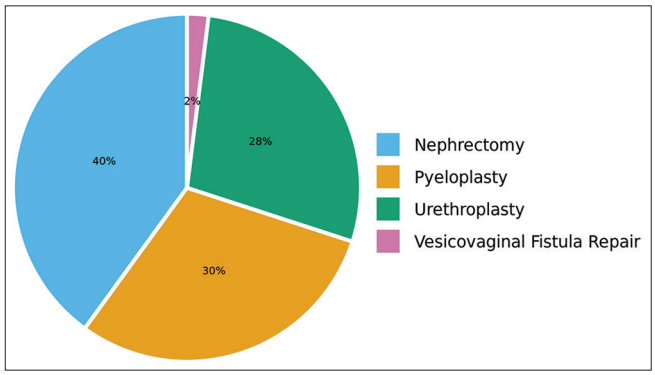

Figure 5: The pie diagram of distribution of type of surgery

Table 5: Distribution of the participants in terms of type of surgery (n=50)

Type of surgery	Frequency	Percentage	95% CI
Nephrectomy	20	40.0	26.7–54.8
Pyeloplasty	15	30.0	18.3–44.8
Urethroplasty	14	28.0	16.7–42.7
Vesicovaginal Fistula Repair	1	2.0	0.1–12.0

Table 6: Comparison of MAP over time between the groups

MAP	Group C		Group P		P-value
Baseline	82.3	5.7	80.1	5.2	0.552
1 min after completion of drug infusion	79.7	5.3	79.1	5.2	0.635
5 min after completion of drug infusion	78.9	4.4	79.7	5.2	0.563
20 min after completion of drug infusion	78.1	4.3	80.0	4.9	0.152
1 min after intubation	96.6	1.8	111.7	4.1	0.019*
3 min after intubation	94.6	1.8	109.1	3.2	0.012*
5 min after intubation	92.3	2.1	104.9	2.4	0.042*
15 min after pneumoperitoneum	105.7	1.6	115.2	2.3	0.023*
30 min after pneumoperitoneum	101.3	1.4	108.0	2.3	0.002*
10 min after release of gas from abdomen	85.6	3.3	95.2	2.6	0.022*
15 min after release of gas from abdomen	81.1	3.2	92.7	2.5	0.01*
P-value for change in MAP over time within each group	<0.01*		<0.01*		
Overall P value for comparison of change in MAP over time between the two groups (generalized estimating equation)	<0.01*				

MAP: Mean arterial pressure

Table 7a: Comparison of change in MAP from baseline to different intervals between the groups

MAP	Group C		Group P		P-value
	Mean reduction	SD	Mean reduction	SD	
Baseline to 1 min after completion of drug infusion	2.5	0.3	1.1	0.2	0.092
Baseline to 5 min after completion of drug infusion	3.3	0.5	3.2	0.4	0.606
Baseline to 20 min after completion of drug infusion	4.2	0.9	3.6	0.6	0.418

MAP: Mean arterial pressure

Table 7b: Comparison of change in MAP from baseline to different intervals between the groups

MAP	Group C		Group P		P-value
	Mean increase	SD	Mean increase	SD	
Baseline to 1 mi after intubation	14.3	3.1	31.5	8.1	0.034*
Baseline to 3 min after intubation	12.3	2.8	28.9	7.5	0.01*
Baseline to 5 min after intubation	10.0	2.4	24.8	6.8	0.009*
Baseline to 15 min after pneumoperitoneum	23.4	4.8	35.1	8.6	0.029*
Baseline to 30 min after pneumoperitoneum	19.1	3.9	27.8	7.1	0.002*
Baseline to 10 min after release of gas from abdomen	3.2	1.4	15.1	3.7	0.042*
Baseline to 15 min after release of gas from abdomen	3.8	1.7	12.5	3.1	0.01*

MAP: Mean arterial pressure

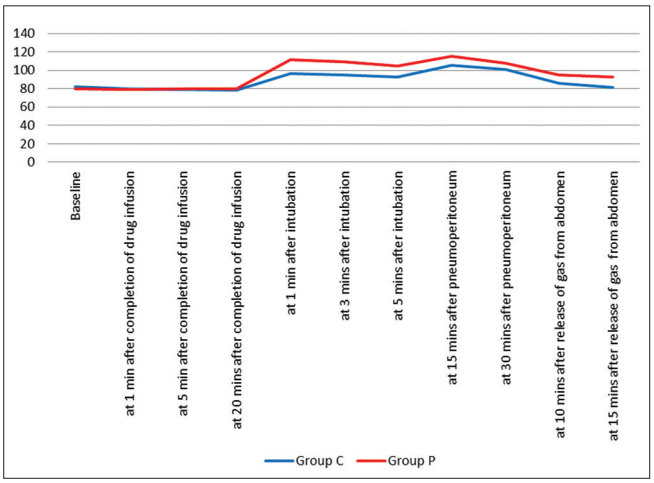

Figure 6: The line diagram depicting the change in MAP overtime in the two groups

About 28.0% of the participants had age: 18–30 years. About 38.0% of the participants had age: 31–40 years. About 26.0% of the participants had age: 41–50 years. About 8.0% of the participants had age: 51–60 Years.

About 54.0% of the participants had gender: male. About 46.0% of the participants had gender: female.

About 44.0% of the participants had ASA: I. About 56.0% of the participants had ASA: II.

About 40.0% of the participants had type of surgery: nephrectomy. 30.0% of the participants had type of surgery: pyeloplasty. About 28.0% of the participants had type of surgery: urethroplasty. About 2.0% of the participants had type of surgery: vesicovaginal fistula repair.

Table 8: Comparison of heart rate over time between the groups

Heart rates	Group C Mean±SD		Group P Mean±SD		P-value
Baseline	92.0	9.1	90.2	8.9	0.318
1 min after completion of drug infusion	62.4	5.6	80.1	12.2	0.01*
5 min after completion of drug infusion	63.4	4.1	80.4	12.3	0.01*
20 min after completion of drug infusion	62.5	4.1	79.9	8.8	0.01*
1 min after intubation	68.3	3.6	118.9	6.7	0.041*
3 min after intubation	65.7	4.4	107.1	8.4	0.035*
5 min after intubation	64.5	3.8	96.3	6.7	0.023*
15 min after pneumoperitoneum	64.5	4.1	106.4	7.1	0.036*
30 min after pneumoperitoneum	66.1	4.2	92.7	7.6	0.033*
10 min after release of gas from abdomen	66.9	4.8	86.9	6.1	0.039*
15 min after release of gas from abdomen	66.8	5.1	83.5	6.8	0.003*
P-value for change in heart rate over time within each group	<0.01*		<0.01*		
Overall P value for comparison of change in heart rate over time between the two groups (generalized estimating equation)	<0.01*				

Table 9a: Comparison of change in heart rate from baseline to different intervals between the groups

Heart rates	Group C		Group P		P-value
	Mean reduction	SD	Mean reduction	SD	
Baseline to 1 min after completion of drug infusion	28.7	7.3	10.1	2.6	0.017*
Baseline to 5 min after completion of drug infusion	28.4	6.9	9.7	2.1	0.004*
Baseline to 20 min after completion of drug infusion	29.0	7.6	10.2	3.2	0.009*

Table 9b: Comparison of change in heart rate from baseline to different intervals between the groups

Heart rates	Group C		Group P		P-value
	Mean reduction	SD	Mean increase	SD	
Baseline to 1 min after intubation	24.4	5.9	28.6	7.4	0.01*
Baseline to 3 min after intubation	26.3	6.1	16.8	3.5	0.047*
Baseline to 5 min after intubation	27.4	6.8	6.1	2.2	0.028*
Baseline to 15 min after pneumoperitoneum	27.5	6.6	16.1	3.6	0.011*
Baseline to 30 min after pneumoperitoneum	26.01	5.7	10.1	2.9	0.006*
Baseline to 10 min after release of gas from abdomen	25.6	4.8	11.1	2.7	0.031*
Baseline to 15 min after release of gas from abdomen	25.9	5.1	9.2	1.9	0.01*

Table 10: Comparison of the two groups in terms of change in plasma cortisol level (µg/dL) over time (n=50)

Plasma Cortisol Level (µg/dL)	Group		P-value for comparison of the two groups at each of the timepoints (Wilcoxon-Mann-Whitney Test)
	C	P	
	Mean (SD)	Mean (SD)	
Before Induction	19.36 (1.49)	19.33 (1.30)	0.984
After Reversal	28.60 (1.21)	32.38 (1.66)	<0.001
P-value for change in Plasma Cortisol Level (µg/dL) over time within each group (Wilcoxon Test)	<0.001	<0.001	
Overall P value for comparison of change in Plasma Cortisol Level (µg/dL) over time between the two groups (Generalized Estimating Equations)	<0.001		

Table 6 shows no statistically significant difference of baseline MAP and MAP following 1, 5, and 20 min following completion of drug infusion between two groups. The MAP of Group C was significantly lower than Group P following intubation, pneumoperitoneum and release of gas from abdomen.

Table 7a shows no statistically significant reduction in MAP from baseline to 1, 5, and 20 min after completion of drug infusion in between the two groups.

Table 7b shows that there is increase in MAP in both the groups from baseline to intubation, pneumoperitoneum,

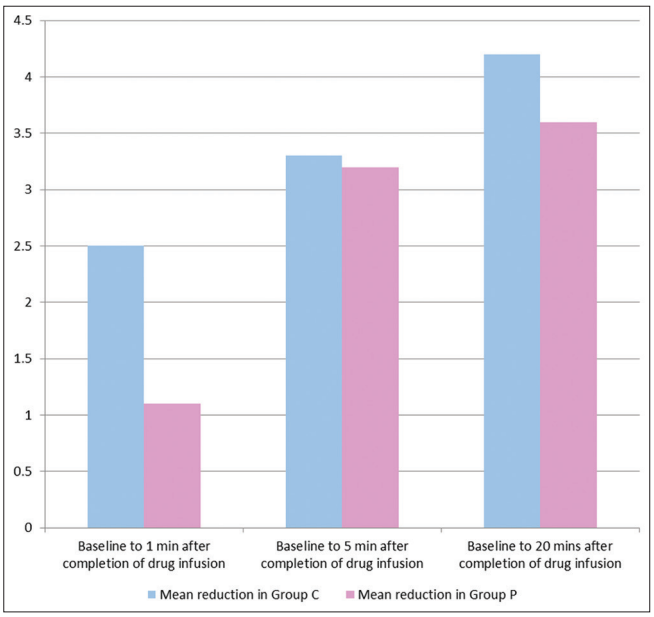

Figure 7: The bar diagram depicting the comparison of change in mean arterial pressure from baseline to drug infusion

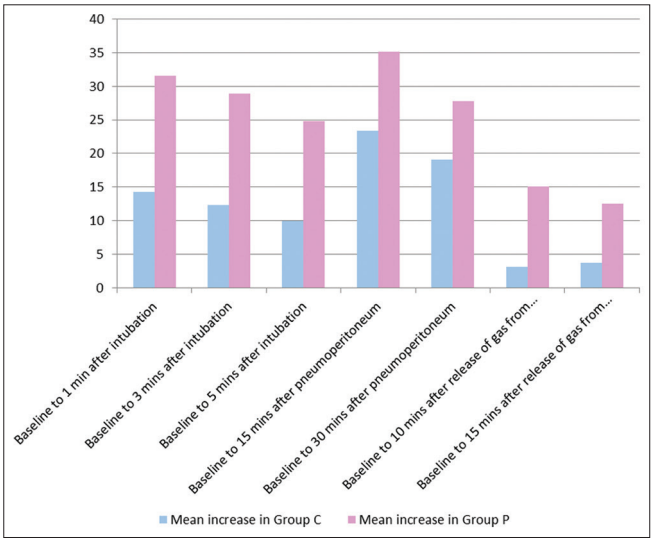

Figure 8: A bar diagram depicting the comparison of mean arterial presure from baseline to intubation, pneumoperitoneum, and release of gas from abdomen

and release of gas from abdomen. Although the mean increase of MAP in Group C was significantly lower than Group P at that timepoints.

Table 8 shows no statistically significant difference of baseline HR between the groups. The HR of Group C was significantly lower than Group P following drug infusion, intubation, pneumoperitoneum, and release of gas from abdomen.

Table 9a shows statistically significant difference in mean reduction of HR from baseline to 1, 5, and

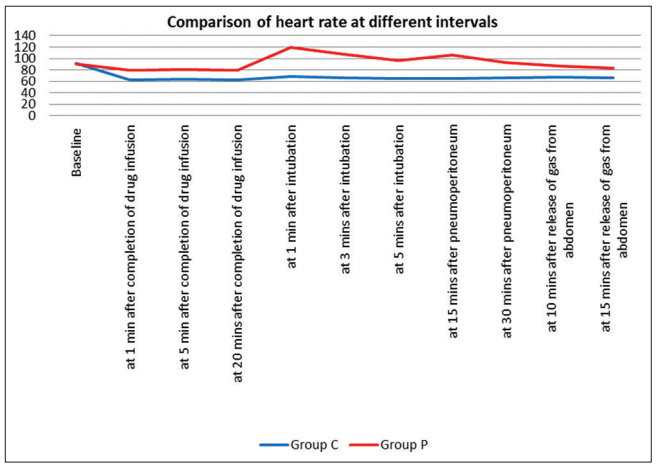

Figure 9: A line diagram depicting the change in heart rate over time in the two groups

20 min after completion of drug infusion in between the two groups.

Table 9b shows statistically significant reduction of HR in Group C from base line to intubation, pneumoperitoneum, and release of gas from abdomen.

Non-parametric tests were used to make statistical inference as data were not normally distributed. Wilcoxon-Mann–Whitney test was used to compare the two groups at each of the timepoints.

The two groups differed significantly in terms of plasma cortisol level (μg/dL) after reversal.

DISCUSSION

The pneumoperitoneum required for laparoscopy causes marked elevation in HR and MAP. Both mechanical and neurohormonal factors contribute to hemodynamic alterations. Clonidine being an alpha-2 adrenergic agonist has been shown to reduce perioperative hemodynamic instability during laparoscopic surgeries.

This prospective randomized double-blind interventional study was carried out in 50 patients to evaluate the effects of intravenous clonidine on hemodynamics and plasma cortisol level during laparoscopic urological surgeries.

In our study, the MAP of Group C was significantly lower than Group P at 1, 3, and 5 min after intubation, 15 and 30 min after pneumoperitoneum, 10 and 15 min after removal of gas from abdomen. The MAP has been significantly increased in both the groups following

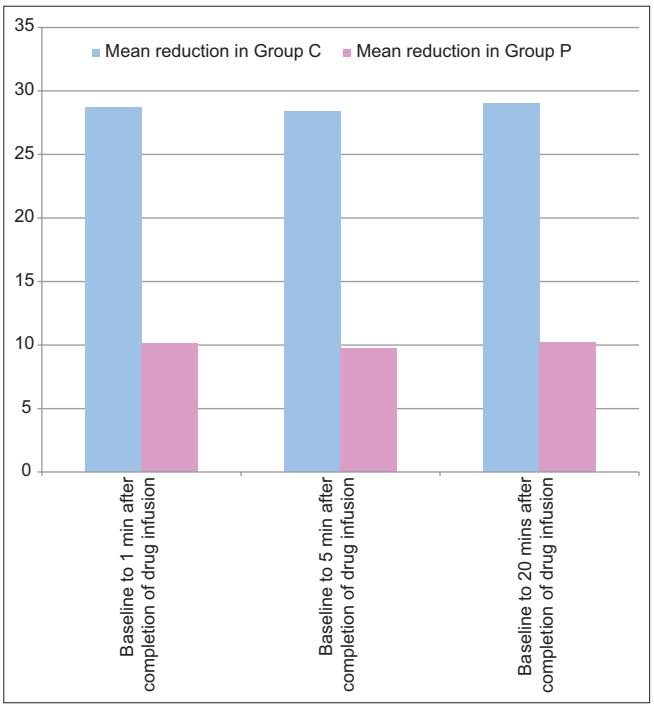

Figure 10: A bar diagram depicting the comparison of change in heart rate from baseline to drug infusion

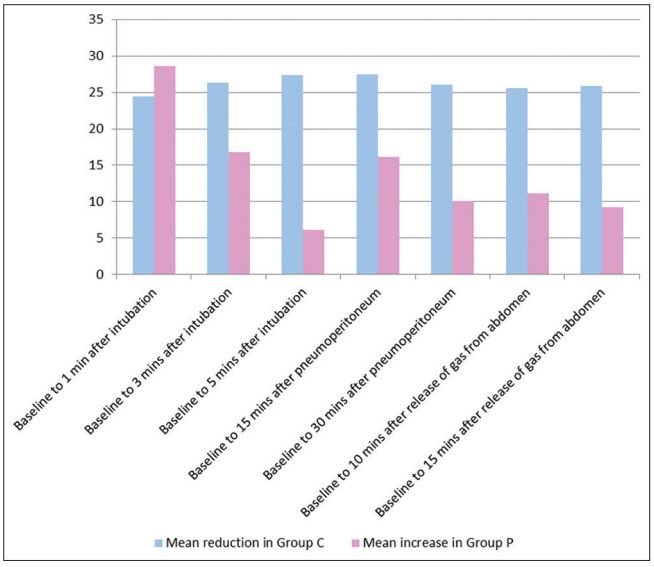

Figure 11: A bar diagram depicting the comparison of change in heart rate from baseline to intubation, pneumoperitoneum, and release of gas from abdomen

intubation, pneumoperitoneum and removal of gas from baseline values. However, the mean increase of MAP in Group C was significantly lower than the mean increase of MAP in Group P at that timepoints.

Málek et al., conducted a comparative study between intravenous and intramuscular clonidine as premedication during laparoscopic cholecystectomy and found a

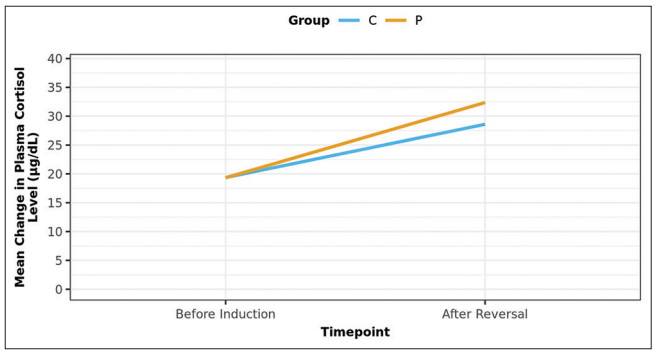

Figure 12: A line diagram depicting the change in plasma cortisol level (µg/dL) over time in the two groups

highly significant drop in the incidence of hypertension (both SBP and DBP) - P<0.001 in both ways of administration.[10]

Gupta et al., performed a randomized controlled trail to study the effect of intravenous Clonidine and intravenous Fentanyl on perioperative hemodynamics during laparoscopic cholecystectomy. They found that intravenous clonidine and intravenous fentanyl both were able to attenuate the perioperative hemodynamic response during laryngoscopy and Pneumoperitoneum. Duration of post-operative analgesia was significantly prolonged in clonidine group compared to Fentanyl group. Postoperatively patients were well sedated and side effects such as nausea, vomiting, and shivering were less in Clonidine group. Intravenous Fentanyl can be used to attenuate the hemodynamic response in normotensive patients were as clonidine will be a better choice in hypertensive patients.[11]

Our study showed that, HR of Group C was significantly lower than Group P at 1, 5 and 20 min after completion of drug infusion, 1, 3, and 5 min after intubation, 15 and 30 min after pneumoperitoneum, and 10 and 15 min after removal of gas from abdomen.

Zhang et al., performed a study named "Effect of Clonidine on Hemodynamic Responses during Laparoscopic Cholecystectomy: A systemic review and meta-analysis" and found that Clonidine intervention significantly reduce HR after pneumoperitoneum and intubation, propofol requirement as well as post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy.[12]

Singh and Arora conducted a study showing that oral clonidine (150 mcg) as a premedication in patients undergoing laparoscopic cholecystectomy results in improved perioperative hemodynamic stability and a

reduction in the requirement of intraoperative anesthetic and post-operative analgesic agents.[13]

In this study, the plasma cortisol level of Group C was significantly lower than Group P after reversal. Although, it has been significantly raised in both groups from baseline values.

Gil-Ad et al., conducted a study named "Effects of Clonidine on plasma beta endorphin, cortisol and growth hormone secretion in opiate addicted subjects" showed that in control subjects Clonidine induced a decrease of 50% in plasma cortisol, whereas in addicted subjects the decrease was not significant.[14]

Stone et al., studied "Hemodynamic and hormonal changes during pneumoperitoneum and Trendelenburg positioning for operative gynecologic laparoscopy surgery" and demonstrated that pneumoperitoneum and Trendelenburg positioning cause statistically significant elevations in stress hormones and concurrently cause decrease in stroke volume and cardiac index. A healthy patient may tolerate these changes but a patient with cardiovascular disease or pulmonary problems may not able to compensate as efficiently.[15]

Sharma et al., performed a study named "A comparison of dexmedetomidine and Clonidine premedication in perioperative hemodynamic stability and postoperative analgesia in laparoscopic cholecystectomy" and found a decrease in HR more in dexmedetomidine group after induction and creation of pneumoperitoneum but no statistically significant difference was found in MAP between two groups.

During our study, we did not observe any side effects such as bradycardia or hypotension probably because of using lower dose of clonidine.[16]

Limitations of the study

- Due to resource constraints plasma cortisol was estimated only 2 times
- Analgesia requirement was not studied
- Study was done on limited group of patients.

CONCLUSION

This study was done to evaluate the effects of intravenous clonidine on hemodynamics and plasma cortisol level during laparoscopic urological surgeries. Here, we have found that clonidine at a dose of 3 mcg/kg administered intravenously before induction attenuated the hemodynamic changes by reducing hormonal stress response and plasma cortisol concentration.

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