

# Surgical management of Ludwig's angina under conscious sedation using intravenous combination of dexmedetomidine and ketamine



Naresh Paliwal<sup>1</sup>, Vibha Pendam<sup>2</sup>, Sunil Lawhale<sup>3</sup>, Nandini Deshpande<sup>4</sup>

<sup>1</sup>Associate Professor, <sup>2</sup>Junior Resident, <sup>3</sup>Professor and Head, <sup>4</sup>Senior Resident, Department of Anaesthesiology, Dr. Panjabrao Deshmukh Memorial Medical College, Amravati, Maharashtra, India

Submission: 20-09-2022

Revision: 22-11-2022

Publication: 01-01-2023

## ABSTRACT

**Background:** Ludwig's angina (LA) is a life-threatening condition, in which there is gangrenous cellulitis of floor of mouth that spreads through facial planes to involve neck region and has the potential to cause airway obstruction. Even though with advent of broad-spectrum antibiotics, its incidence has decreased considerably, the anesthetic management of patients, particularly children, undergoing drainage for LA group STILL remains a challenging task. **Aims and Objectives:** The aim of this study was to test the efficacy and safety of intravenous combination of dexmedetomidine and ketamine (DEXKET) for the drainage of abscess in patients having LA. **Materials and Methods:** This was a prospective study, in which 40 cases having LA and posted for Abscess drainage were included on the basis of a redefined inclusion and exclusion criteria. Abscess drainage was done under anesthesia using DEXKET as the only intravenous drug. DEXKET was prepared by mixing dexmedetomidine 0.5 mcg/kg along with ketamine 1 mg/kg in a 5 ml syringe and then diluted until 5 ml with distilled water. This was given as bolus dose. Drainage was accomplished under IV (DEXKET) sedation. **Results:** In this study, there were 28 males and 12 females with a M: F ratio of 1:0.42. The mean age of male and female patients was found to be  $38.35 \pm 10.58$  and  $36.41 \pm 11.37$  years, respectively. Dental caries was the most common cause leading to LA which was seen in 32 (80%) patients. There were no episodes of significant bradycardia, hypotension or desaturation during surgical procedure, as well as in post-operative period. The procedure could be accomplished without any additional doses of DEXKET. Two of the patients (5%) had post-operative nausea and vomiting. **Conclusion:** Drainage under sedation by intravenous combination of DEXKET is found to be an effective approach for drainage of abscess in cases of LA.

**Key words:** Ludwig's angina; Dexmedetomidine and ketamine; Sedation; Analgesia; Visual analog scale

## INTRODUCTION

Ludwig's angina (LA) is a rapidly progressive cellulitis of floor of mouth that has got a considerable morbidity as well as mortality if not treated aggressively.<sup>1</sup> This cellulitis and inflammatory process rapidly progresses to involve submandibular, sublingual, as well as submental spaces. The rapidly progressive cellulitis may also give rise to

abscess formation in floor of mouth as well as deep neck spaces. Common predisposing factors include poor dental hygiene, infections of 2<sup>nd</sup> and 3<sup>rd</sup> mandibular molar teeth, peritonsillar abscess, and mandibular fractures. In many cases, no predisposing factor may be identified. It is more commonly seen in men as compared to women. Individuals with low socioeconomic status were found to be commonly affected due to poor oral hygiene. The

### Access this article online

**Website:**

<http://nepjol.info/index.php/AJMS>

**DOI:** 10.3126/ajms.v14i1.48512

**E-ISSN:** 2091-0576

**P-ISSN:** 2467-9100

Copyright (c) 2023 Asian Journal of Medical Sciences



This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

### Address for Correspondence:

Dr. Nandini Deshpande, Senior Resident, Department of Anaesthesiology, Dr. Panjabrao Deshmukh Memorial Medical College, Amravati, Maharashtra, India. **Mobile:** +91-8890287845. **E-mail:** nandini.510@gmail.com

other predisposing factors include recent dental extraction, immunosuppressive drugs, diabetes mellitus, oral mucosal laceration, and patients having immunodeficiency.<sup>2</sup>

Irrespective of the cause LA is almost always rapidly progressive and can involve floor of mouth as well as deep neck spaces rapidly thereby endangering airway patency. The progress may be faster in children. The common clinical presentation of patients with LA includes fever, lethargy, swollen neck, restricted neck movements, elevated tongue, trismus, odynophagia, drooling of saliva and in severe cases, severe dyspnea, and respiratory distress in the form of shallow and irregular breathing with intercostal and subcostal retractions may be seen.<sup>3</sup>

Early diagnosis and appropriate parenteral broad-spectrum antibiotics may prove to be effective in the early stages and will obviate the need for surgical interventions. If there is ANY delay in diagnosing and giving parenteral antibiotics, then the cellulitis may rapidly progress through facial planes to involve deep neck spaces and may rapidly compromise airway. In all such cases, immediately securing airway followed by surgical drainage of abscess must be done on emergency basis. Any delay in surgical intervention in these cases may rapidly prove fatal.<sup>4</sup>

From the perspective of anesthesiologist, the management of patients with LA can prove to be a nightmare. There are chances of difficult airway causing difficulties in intubation even by experienced anesthesiologists. In many cases, emergency tracheostomy is done to secure airway. With the advent of fiberoptic intubation, most of the experienced are going for fiberoptic intubation in these cases.<sup>5</sup> Given the difficulty in assessing airway as well as difficulty in intubation in these cases for surgery under general anesthesia, there have been attempts for surgical drainage of cases of LA under conscious sedation. There are case reports which described surgical management of these cases using under sedation with Dexmedetomidine.<sup>6</sup>

Dexmedetomidine is an alpha-2-adrenergic agonist drug which is effective in controlling perioperative pain considerably. It is a sedative drug with significant analgesic, opioid sparing, as well as sympatholytic properties. It does not cause significant respiratory depression. Dexmedetomidine in combination with ketamine can be used for short surgical procedures, such as drainage of abscess as seen in LA, under sedation without need for intubation.<sup>7</sup>

Combination of dexmedetomidine and ketamine (DEXKET) is being increasingly used for conscious sedation for procedures such as septoplasty and tympanoplasty. Dexmedetomidine alone is found to have variable results for procedures to be done under conscious sedation.<sup>8</sup>

Combination of DEXKET is therefore, being extensively used for procedures done under conscious sedation. When used together, dexmedetomidine counteracts the side-effects of ketamine such as tachycardia, hypertension, and increased salivation. On the other hand, ketamine prevents the bradycardia and hypotension associated with the use of dexmedetomidine.<sup>9</sup>

We undertook this study of patients with LA undergoing surgical drainage under conscious sedation by intravenous administration of combination of DEXKET. To the best of our knowledge, there is no other published study which has dealt with undertaking surgical drainage of LA under conscious sedation by combination of DEXKET.

### Aims and objectives

The aim of this study was to test the efficacy and safety of intravenous combination of dexmedetomidine and ketamine (DEXKET) for the drainage of abscess in patients having LA.

## MATERIALS AND METHODS

This was a prospective study, in which 40 patients with LA and posted for abscess drainage were included on the basis of a predefined inclusion and exclusion criteria mentioned below. The study was conducted in the department of anesthesiology Dr. Panjabrao Deshmukh Memorial Medical College, Amravati, India. The Institutional Ethical Committee approved the study and informed consent was obtained either from the adult patients or the parents in case of pediatric patients. Demographic details such as age and gender were noted. Pre-anesthetic evaluation as well as assessment of airways were done. Basic laboratory investigations such as complete blood count, random blood sugar, liver function test, renal function test, chest X-ray, and electrocardiogram were done in all cases. The entire procedure was explained to the patient in their own local language. All the patients were reviewed again before surgery. Pre-operative direct laryngoscopy for airway evaluation was not possible due to associated pain and swelling. Difficult intubation cart (fiberoptic bronchoscope, proper size LMA and ET tubes, cricothyrotomy kit, emergency tracheostomy tray, different types of laryngoscope blades, bougies, etc.) and proper functioning suction machine were kept ready.

Patients were positioned either in lateral or supine position with pillow under the shoulders (to utilize oropharyngeal dead space as a reservoir in case the abscess ruptures from inside). Nasal prongs with Oxygen with a flow rate of 2–3 lit/min were connected along with multipara monitoring devices. DEXKET was prepared by mixing dexmedetomidine

0.5 mcg/kg along with ketamine 1 mg/kg in a 5 ml syringe and then diluted with distilled water until a total volume of 5 ml is obtained. After securing the IV line with 20G Neocan, DEXKET was given as slow bolus over a minute until the patient got sedated. During this period, patients were assessed every 3 min using Ramsay sedation score (1=agitated, restless; 2=cooperative, tranquil; 3=responds to verbal command while sleeping; 4=brisk response to glabellar tap or loud voice while sleeping; 5=sluggish response to glabellar tap or loud voice; and 6=no response to glabellar tap or loud voice). When the RSS of 3 is reached, surgeons were asked to do a graded puncture after initially aspirating with wide bore needle to reduce the bulk. Nothing else than Combination of DEXKET was given to maintain the airway tone and reflexes. Slight response to initial stimulation in one or two cases was accepted for safety of the patient.

Patients were monitored for pulse rate, BP, RR, pain by visual analog scale (VAS) score, sedation score during surgery (every 3 min), and immediate post-operative period (every 15 min for 1 h and half hourly thereafter until next 5 h). Side-effects if any were also documented. The presence and severity of pain was assessed using VAS Score. Rescue analgesia was given by diclofenac iv 0.15 mg/Kg injection AND if VAS score was found to be more than 4. Severity of post-operative pain, time to first request of rescue analgesia (duration of analgesia), post-operative sedation, and analgesic requirement during first 24 h was documented. SSPS 21.0 was used for statistical analysis and  $p < 0.05$  was taken as statistically significant.

**Inclusion criteria**

The following criteria were included in the study:

1. All patients with LA posted for abscess drainage
2. Those who gave informed written consent to be part of study
3. ASA Grade I and II.

**Exclusion criteria**

The following criteria were excluded from the study:

1. Patients who refused consent
2. Patients with ASA grade III and IV

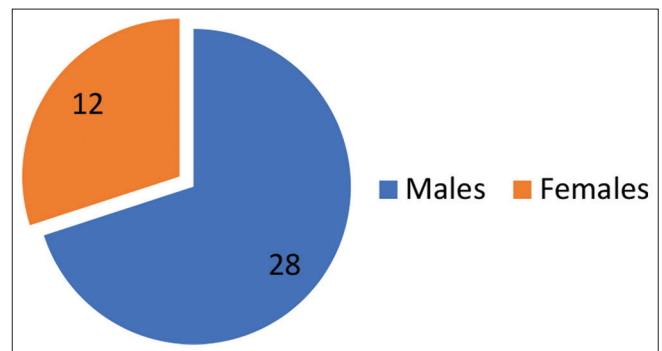
3. Hemodynamically unstable patients or patients having uncontrolled systemic illnesses such as diabetes, hypertension, or chronic obstructive airway diseases
4. Pregnant patients.

**RESULTS**

This was a prospective study, in which 40 cases of LA posted for abscess drainage were included. Out of 40 cases, there were 28 males and 12 females with an M: F ratio of 1:0.42 (Figure 1).

The analysis of patients on the basis of age showed that most common affected age group was 31–40 years (35%) followed by 41–50 years (27.50%). Seven (17.50%) and 5 (12.50%) patients were seen between 51 and 60 years and 21–30 years, respectively. Only three patients (7.50%) were below 20 years of age. There was no patient above 60 years in our study. The mean age of male and female patients was found to be  $38.35 \pm 10.58$  and  $36.41 \pm 11.37$  years, respectively. The mean age was found comparable with no statistically significant difference ( $P = 0.606$ ) (Table 1).

The analysis of the patients on the basis of etiology showed that dental caries was the most common cause leading to LA and was seen in 32 (80%) patients. The other causes included impacted 3<sup>rd</sup> molar (20%), gingivitis (12.50%), and post tooth extractions sepsis (7.50%). In 2 (5%) cases, submandibular gland abscess led to LA (Table 2).



**Figure 1:** Gender distribution of the studied cases

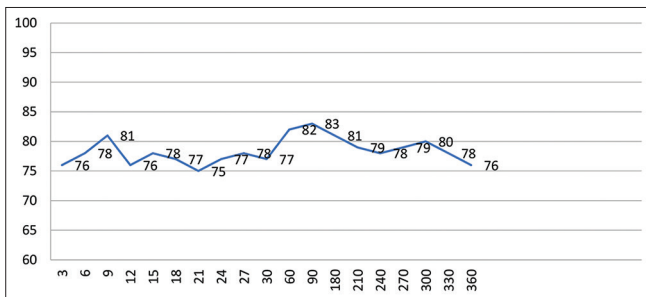
**Table 1: Age distribution of the studied cases**

Age in years	Males		Females	
	Number of cases	Percentage	Number of cases	Percentage
<20 years	1	2.50	2	5.00
21–30 years	4	10.00	1	2.50
31–40 years	10	25.00	4	10.00
41–50 years	8	20.00	3	7.50
51–60 years	5	12.50	2	5.00
>60 years	0	0.00	0	0.00
Total	28	70	12	30
Mean age	38.35±10.58 years		36.41±11.37 years	

Patients were analyzed for ASA Grades. Among males, there were 22 patients (55%) with ASA Grade I and remaining six patients (15%) were ASA Grade II. Among females, ten patients (25%) were ASA Grade I and remaining two patients (5%) were ASA Grade II. The ASA grades in male and female patients were found comparable with no statistically significant difference ( $p>0.05$ ) (Table 3).

In our study, all the patients reached RSS of 3 at the end of bolus infusion and no additional dose of DEXKET was required. The mean duration of surgical procedure was found to be  $21.42\pm 8.72$  min from incision to completion of procedure.

Heart rate, systolic blood pressure and diastolic blood pressure, mean arterial pressure,  $SPO_2$ , and respiratory rates were monitored every 3 min until the surgical procedure was over. After surgical procedure was over, patients were monitored for hemodynamic changes  $\frac{1}{2}$  hourly until 6 h. There were no episodes of significant bradycardia, hypotension, or desaturation during surgical procedure as well as in post-operative period and the patients remained calm and responded to verbal commands during procedure. The mean Ramsay sedation scores were monitored throughout the procedure and in post-operative period until patients came out of sedation (Figures 2-8).



**Figure 2:** Intraoperative and post-operative mean heart rate in studied cases

Etiology of LA	Number of cases	Percentage
Caries tooth	32	80.00
Post tooth extraction sepsis	3	7.50
Gingivitis	5	12.50
Submandibular gland abscess	2	5.00
Impacted 3 <sup>rd</sup> molar	8	20.00

Age in years	Males		Females	
	Number of cases	Percentage	Number of cases	Percentage
ASA I	22	55.00	10	25.00
ASA II	6	15.00	2	5.00
Total	28	70.00	12	30.00
Mean age	38.35±10.58 years		36.41±11.37 years	

The analysis of VAS scores in immediate post-operative period as well as until 6 h postoperatively showed that there was no pain in patients of either group until 30 min after surgery. After 90 min, patients in Group D were found to have less severe pain as assessed by VAS scores as compared to patients in group and the difference was found to be statistically significant ( $P<0.05$ ). However, at 6 h postoperatively, the severity of pain was found to be comparable in both the groups with no statistically significant difference between patients of both the groups ( $P>0.05$ ) (Table 4).

The patients were followed up for total requirement of rescue analgesics in first 24 h which was given in the form of intravenous injections of diclofenac sodium (Table 5).

Two patients (5%) had post-operative nausea and vomiting which were treated by intravenous ondansetron. There was no nausea and vomiting in 38 (95%) patients (Table 6).

## DISCUSSION

Airway management of patients with LA can be challenging due to anticipated difficult airway. The situation is complicated by the fact that unlike in other patients, it is also difficult to make a pre-operative assessment of airway in patients with LA.<sup>10</sup> In emergency situation, the intubation many times becomes tricky due to subglottic edema, trismus, and superiorly pushed tongue due to cellulitis of floor of mouth. The alternative methods of securing airway in these cases include blind nasal intubation and fibreoptic intubation.<sup>11</sup> In emergency situations, where it is not possible to do intubation due to difficult airway, emergency tracheostomy may also be done as a life-saving procedure.<sup>2</sup> Although fibreoptic intubation is being increasingly done in cases with LA, the facilities for fibreoptic intubation are not available everywhere. Since surgical drainage of abscess is the definitive surgical management in cases of LA who fail to respond to parenteral antibiotics and in whom abscess is identified on the basis of imaging, the anesthetic management of patients undergoing drainage becomes important.<sup>12</sup> Though various intravenous as well as inhalational anesthetic drugs can be used for general anesthesia in these cases, difficult airway becomes an

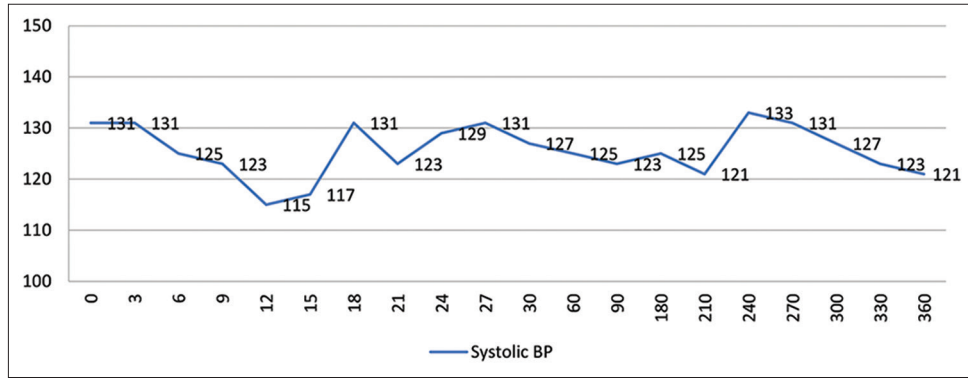


Figure 3: Intraoperative and post-operative systolic blood pressure

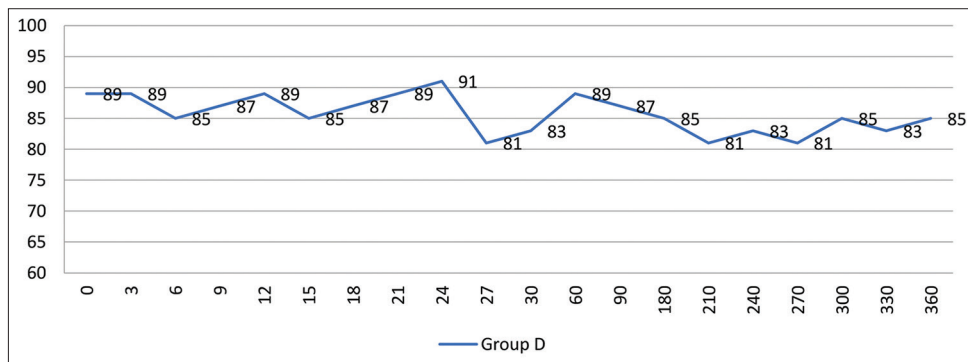


Figure 4: Intraoperative and post-operative diastolic blood pressure

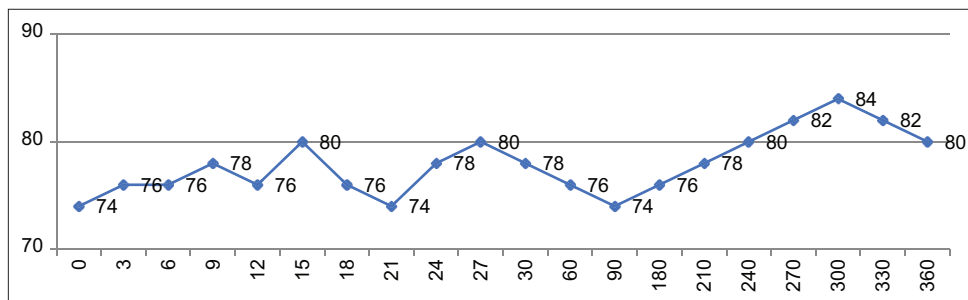


Figure 5: Intraoperative and post-operative mean arterial pressure in studied cases

Duration	Mean VAS score
Immediate post-operative period	00
30 min	00
45 min	1.84±0.48
60 min	2.82±0.72
120 min	3.22±0.94
150 min	3.12±0.90
180 min	3.68±0.96
4 h	4.42±1.12
6 h	4.12±0.98

Doses of Inj. diclofenac	Number of patients	Percentage
1 (75 mg)	32	80.00
2 (150 mg)	8	20.00
3 (225 mg)	0	0.00

Post-operative nausea and vomiting	Group Dn (30) (%)
Present	2 (5)
Absent	38 (95)

important hindrance to general anesthesia in these cases. Therefore, drainage of abscess under conscious sedation can be considered as an excellent alternative to general anesthesia and should be utilized whenever feasible.<sup>13</sup>

In our study, we used combination of DEXKET for conscious sedation in patients having LA and undergoing drainage of abscess. In our study, there was a male predominance and



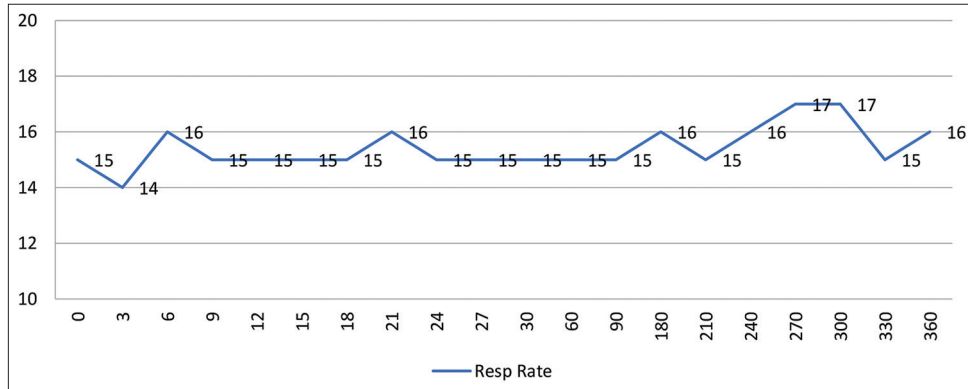


Figure 6: Intraoperative and post-operative respiratory rates in studied cases

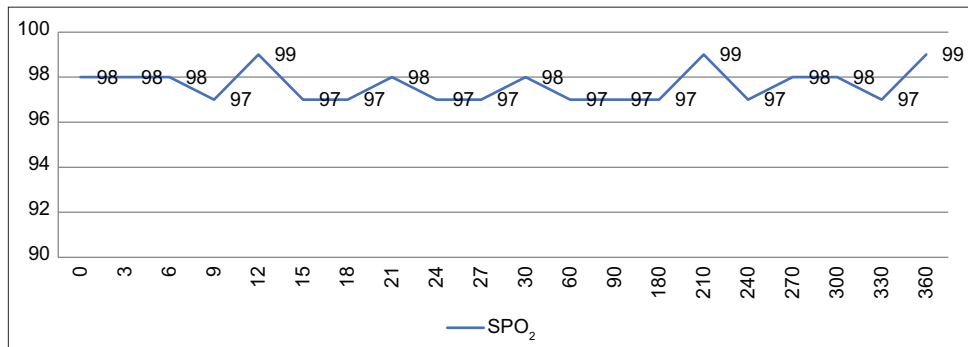


Figure 7: Intraoperative and post-operative SPO<sub>2</sub> in studied cases

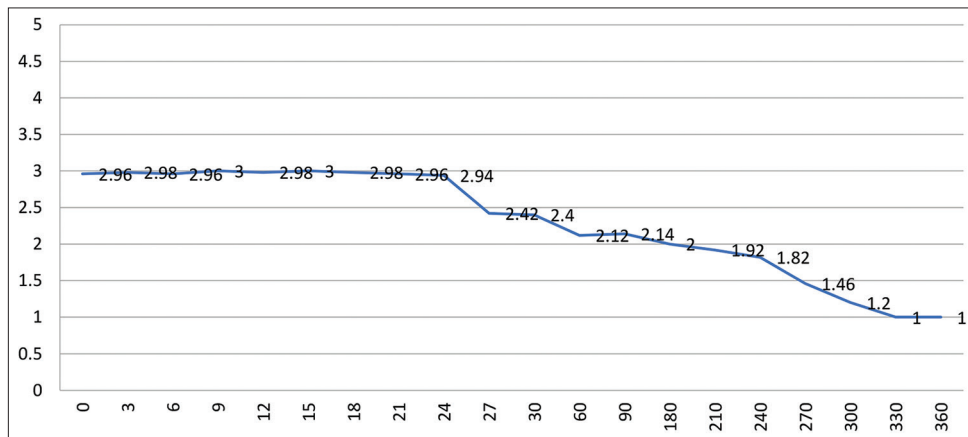


Figure 8: Ramsay sedation score in studied cases

the mean age of male and female patients was found to be  $38.35 \pm 10.58$  and  $36.41 \pm 11.37$  years, respectively. Singh et al., conducted a study of 30 patients presenting with clinical diagnosis of LA.<sup>14</sup> The authors found that the most common age group was third decade of life. Caries tooth was most common etiology followed by gingivitis. Difficulty in swallowing and pain in neck was the most common symptoms in the studied cases. The study concluded that that surgical management should be done at earliest in presence of respiratory difficulty as medical treatment alone can prove to be dangerous. The etiological profile of the patients in this

study was found to be similar to our study. Similar etiological profile of patients with LA was also reported by the authors such as Wolfe et al.,<sup>15</sup> and Allareddy et al.<sup>16</sup>

We used combination of DEXKET as an intravenous bolus dose and the whole procedure (surgical drainage of abscess) could be accomplished without any need to give additional Sedation. There were no adverse hemodynamic events during or after surgical procedure. Various authors have used combination of DEXKET for short surgeries to be done under sedation. Two patients (5%) had post-operative nausea

and vomiting, whereas there was no nausea and vomiting in 38 (95%) patients. Many authors have used combination of DEXKET for the purpose of sedation during short surgical procedure. Tobias JD undertook a review study to find out the efficacy of combination of DEXKET for procedural sedation.<sup>17</sup> In this study, the author HAS reviewed four studies and concluded that when used together, dexmedetomidine may prevent the tachycardia, hypertension, salivation, and emergence phenomena from ketamine, whereas ketamine may prevent the bradycardia and hypotension, which has been reported with dexmedetomidine. The study concluded that there is considerable literature available to show favorable utility of combination of ketamine and dexmedetomidine for procedural sedation. Similar findings have also been reported by the authors such as Scher and Gitlin<sup>18</sup> and Sado-Filho et al.<sup>19</sup>

### Limitations of the study

Relatively, small size was limitation of this study. A large study comprising larger number of patients would certainly validate the findings of this study.

## CONCLUSION

Combination of DEXKET as an intravenous bolus is effective for conscious sedation and analgesia for drainage of abscess in cases of LA. It has been found to have an excellent safety profile in terms of intraoperative as well as immediate post-operative hemodynamic and negligible side effects.

## ACKNOWLEDGEMENT

The authors would like to acknowledge teaching faculties and staff of Department of Anesthesiology, Dr. Panjabrao Deshmukh Memorial Medical College Amravati (MS) India for extending their valuable support in undertaking this study.

## REFERENCES

- Parker E and Mortimore G. Ludwig's angina: A multidisciplinary concern. *Br J Nurs*. 2019;28(9):547-551. <https://doi.org/10.12968/bjon.2019.28.9.547>
- Kovalev V. A severe case of Ludwig's angina with a complicated clinical course. *Cureus*. 2020;12(4):e7695. <https://doi.org/10.7759/cureus.7695>
- Candamourty R, Venkatachalam S, Babu MR and Kumar GS. Ludwig's angina-an emergency: A case report with literature review. *J Nat Sci Biol Med*. 2012;3(2):206-208. <https://doi.org/10.4103/0976-9668.101932>
- Miller CR, Von Crowns K and Willoughby V. Fatal Ludwig's angina: Cases of lethal spread of odontogenic infection. *Acad Forensic Pathol*. 2018;8(1):150-169. <https://doi.org/10.23907/2018.011>
- Kulkarni AH, Pai SD, Bhattarai B, Rao ST and Ambareesha M. Ludwig's angina and airway considerations: A case report. *Cases J*. 2008;1(1):19. <https://doi.org/10.1186/1757-1626-1-19>
- Kaur M and Singh PM. Current role of dexmedetomidine in clinical anesthesia and intensive care. *Anesth Essays Res*. 2011;5(2):128-133. <https://doi.org/10.4103/0259-1162.94750>
- Dowdy RA, Emam HA and Cornelius BW. Ludwig's angina: Anesthetic management. *Anesth Prog*. 2019;66(2):103-110. <https://doi.org/10.2344/anpr-66-01-13>
- Naaz S and Ozair E. Dexmedetomidine in current anaesthesia practice-a review. *J Clin Diagn Res*. 2014;8(10):GE01-GE04. <https://doi.org/10.7860/JCDR/2014/9624.4946>
- Amornyotin S. Use of a combination of ketamine and dexmedetomidine (ketodex) in different clinical cases. *J Addict Med Ther Sci*. 2020;6(1):41-44. <https://doi.org/10.17352/2455-3484.000036>
- Mohamad I, Zulkifli S, Soleh M and Rahman R. Ludwig's angina: The importance of oral cavity examination in patients with a neck mass. *Malays Fam Physician*. 2012;7(2-3):51-53. <https://doi.org/10.4103/0019-5049.167486>
- Sujatha MP, Madhusudhana R, Amrutha KS and Nupoor N. Anaesthetic management of Ludwig's angina with comorbidities. *Indian J Anaesth*. 2015;59(10):679-681. <https://doi.org/10.4103/0019-5049.167486>
- Edetanlen BE and Saheeb BD. Comparison of outcomes in conservative versus surgical treatments for Ludwig's angina. *Med Princ Pract*. 2018;27(4):362-366. <https://doi.org/10.1159/000490740>
- Kangabam SD and Heisnam I. Ludwig's angina and anaesthetic difficulties: A case report. *J Evol Med Dent Sci*. 2015;4(28):4916-4919. <https://doi.org/10.14260/jemds/2015/716>
- Singh H, Singh R, Goyal G, Dhillon V, Arora V and Sarkar A. Ludwig's angina: Analysis of clinical features and their management strategy: A study of 30 patients. *Int J Otorhinolaryngol Head Neck Surg*. 2020;6(10):1830-1836. <https://doi.org/10.18203/issn.2454-5929.ijohns20204184>
- Wolfe MM, Davis JW and Parks SN. Is surgical airway necessary for airway management in deep neck infections and Ludwig angina? *J Crit Care*. 2011;26(1):11-14. <https://doi.org/10.1016/j.jccr.2010.02.016>
- Allareddy V, Rampa S, Nallaih RP and Allareddy V. Longitudinal discharge trends and outcomes after hospitalization for mouth cellulitis and Ludwig angina. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2014;118(5):524-531. <https://doi.org/10.1016/j.o000.2014.06.003>
- Tobias JD. Dexmedetomidine and ketamine: An effective alternative for procedural sedation? *Pediatr Crit Care Med*. 2012;13(4):423-427. <https://doi.org/10.1097/PCC.0b013e318238b81c>
- Scher CS and Gitlin MC. Dexmedetomidine and low-dose ketamine provide adequate sedation for awake fiberoptic intubation. *Can J Anaesth*. 2003;50(6):607-610. <https://doi.org/10.1007/BF03018650>
- Sado-Filho J, Corrêa-Faria P, Viana KA, Mendes FM, Mason KP, Costa LR, et al. Intranasal dexmedetomidine compared to a combination of intranasal dexmedetomidine with ketamine for sedation of children requiring dental treatment: A randomized clinical trial. *J Clin Med*. 2021;10(13):2840. <https://doi.org/10.3390/jcm10132840>

**Authors Contribution:**

**NP**- Concept and design of the study; interpreted the results, prepared first draft of manuscript and critical revision of the manuscript; **VP**- Statistically analyzed and interpreted; reviewed the literature and manuscript preparation; **SL**- Design of the study, statistically analyzed and interpreted, preparation of manuscript and revision of the manuscript; **ND**- Coordination of the overall study.

**Work attributed to:**

Department of Anaesthesiology, Dr. Panjabrao Deshmukh Memorial Medical College, Amravati, Maharashtra, India.

**Orcid ID:**

Dr. Naresh Paliwal - <https://orcid.org/0000-0001-7179-9196>

Dr. Vibha Pendam - <https://orcid.org/0000-0002-2911-7152>

Dr. Sunil Lawhale - <https://orcid.org/0000-0002-3261-4555>

Dr. Nandini Deshpande - <https://orcid.org/0000-0003-0818-1590>

**Source of Support:** Nil, **Conflicts of Interest:** None declared.