

EFFECTIVENESS OF KETAMINE NEBULIZATION IN POSTOPERATIVE SORE THROAT: A RANDOMISED PROSPECTIVE STUDY

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Abstract

Background: Sore throat is a common post-operative complication following intubation. The incidence of post-operative sore throat (POST) is 21%–65%. It produces significant agony and annoyance to the patient. The aim of the study is to see if nebulized ketamine reduces POST. **Materials and Methods:** In our study, 80 patients of ASA grade I–II, aged 18-50 yrs undergoing GA were randomly divided into two groups. Group S received saline nebulization 3.0 ml and group K received ketamine 1 mg/kg with 3.0 ml of normal saline nebulization for 10 min prior to induction. The POST and hemodynamic recording were done pre-nebulization, pre induction, immediately after extubation and at 2, 4, 6, 8, 12 and 24 hour post-operatively. POST was graded on a four point scale (0–3). Ramsay sedation score was measured at 1 hour post extubation in two groups. **Result:** The overall incidence of POST was 39%; 24 patients (60%) in saline and 7 patients (18%) in ketamine group experienced POST. The ketamine nebulization attenuated POST at 2 h and 4 h post-operatively ($P < 0.05$). The primary outcome was incidence of POST at 4 h; 13 patients in group S versus 3 patients in group K experienced POST at 4 h ($P = 0.002$). The moderate sore throat occurred in 6 patients in group S and 2 in group K at 2 h ($P = 0.021$). **Conclusion:** Ketamine nebulization significantly attenuate the incidence and severity of POST, with no adverse effects.

INTRODUCTION

Postoperative sore throat (POST) is a common incidence after general anaesthesia with tracheal intubation despite all efforts made over years. Incidence of sore throat is about 21% to 65% in different studies worldwide.^[1,2] Patients have rated it as the eighth most adverse effect in the postoperative period.^[3] In most cases it resolve spontaneously, if left unresolved, it produces significant agony, dissatisfaction and discomfort to the patients, affects postoperative recovery, increase the length of stay and cost of care and delay their normal routine activities.^[4,5] Nebulization therapy is widely used and highly recommended to attenuate post operative sore throat.

Mechanical injury during intubation, damage to mucosa due to pressure from the endotracheal (ET) tube cuff, dehydration of the mucosa, suctioning and surgical manipulation of airway are probable etiology for POST. Numerous non-pharmacological and pharmacological studies done in past for attenuating POST with variable success rate. Most

commonly used non-pharmacological methods are small size endotracheal tubes, lubrication of tracheal cuff with jelly, gentle laryngoscopy after complete muscle relaxation, intra cuff pressure at or below 20cm H₂O, gentle suctioning and smooth extubation with fully deflated ET tube cuff.^[6] The pharmacological methods used to reduce POST include use of beclomethasone gel, gargling with azulesulphonate, ketamine and licorice.^[7]

Ketamine is an N- methyl- D- aspartate (NMDA) receptor antagonist and has been used in gargle form for reducing the incidence and severity of POST due to its anti-nociceptive and anti-inflammatory effects.^[8] The advantage of Ketamine nebulization over gargle are; it spares the patient from the bitter taste of ketamine, easy way of administration, smaller volume is required, risk of aspiration is less if accidentally swallowed, hence it increase patient cooperation.

The main objective of this study is to evaluate the role of nebulized ketamine for attenuation of post-operative sore throat with normal saline group in

patients undergoing surgeries under General Anaesthesia (GA) with tracheal intubation.

MATERIALS AND METHODS

This prospective, randomized, double blind, single centre study was conducted during the period 2021-2022 after approval of Institutional Ethics Committee of India (Reg. No.- ECR/635/INST/GJ 2014) dated January 24, 2019 and registering the trial with the Clinical Trial Registry of India (CTRI/2022/04/041732). The authors comply with Declaration of Helsinki (2013) & relevant national laws & regulations. Written informed consent was obtained from each participant.

Randomization and allocation concealment

Randomization sequence was created using Excel 2007 (Microsoft, Redmond, WA, USA) with a 1:1 allocation by an independent doctor. The allocation sequence was concealed from the researcher (JR) enrolling and assessing participants in sequentially numbered, opaque, sealed and stapled envelopes based on computer-generated random numbers. Corresponding envelopes were opened only after the enrolled participants completed all baseline assessments and it was time to allocate the intervention.

All Patients were randomly assigned into two equal groups (n = 40). Group S received saline nebulization 3.0 ml and group K received ketamine 1mg/kg with 3.0 ml of normal saline nebulization for 10 min prior to induction. Both patients and the attending anaesthesiologist were unaware of the group allocation.

80 patients of either sex, aged 18-50 years, of American Society of Anaesthesiologists physical status (ASA) I-II, scheduled for elective surgeries under General Anaesthesia with tracheal intubation were enrolled in the study. A history of pre-operative sore throat, oral and nasal surgeries, upper respiratory tract infection, asthma, chronic obstructive pulmonary disease, head and neck surgeries, pregnant females, mallampati grade >2, known allergies to study drug and those who required more than two attempt at intubation were excluded from the study.

Study Protocol

A detailed pre-anaesthetic assessment of each case was done. On the day of surgery, intravenous line was secured with 20G cannula, standard monitors like NIBP, pulse oximeter and continuous ECG was applied to all patients. After recording of baseline vitals, all patients were premedicated with Inj. Glycopyrrolate (4 µg/kg) I.V., Inj. Ondansetron (80 µg/kg) I.V., Inj. Ranitidine (1 mg/kg) I.V., Inj. Midazolam (0.03 mg/kg) I.V and Inj. Tramadol (1 mg/kg) I.V. Group K (Ketamine group): The patients were nebulized with 1 mg/kg ketamine with normal saline (making total volume 3ml), 10 min. prior to induction and Group S (Saline group): The patients were nebulized with 3 ml of normal saline,

10 min. prior to induction. Pre-Oxygenation was done with 100% O₂ with face mask for 3 minutes. Induction was done with Inj. Sodium thiopentone (5 mg/kg) and Inj. Succinylcholine (2 mg/kg). IPPV was given with 100% O₂ and after adequate relaxation (≈60 seconds) laryngoscopy was done using standard Macintosh blade. Oral Intubation was done with appropriate sized, disposable, high volume low pressure, portex cuffed endotracheal tube. Anaesthesia will be maintained with O₂ (33%) and supplemented with Isoflurane (0.5-1.0%) and Inj. Vecuronium bromide (0.02 mg/kg). After completed surgery, neuromuscular blockage was reversed with Inj. Neostigmine (0.05 mg/kg) and Inj. Glycopyrrolate (0.004 mg/kg) intravenously. In the post-anaesthesia care unit, a blinded observer was monitored following data of all the patients: Postoperative sore throat at 2 h, 4 h, 8 h, 12 h and 24 h by its grading on four point scale, Ramsay sedation score at 1 h post extubation and side effects e.g. nausea, vomiting, agitation etc.

Sore throat assessment and hemodynamic monitoring were done at pre- nebulization (baseline parameters before nebulization of patient), pre- induction (parameters after nebulization and just before induction of GA), post extubation (0 hr), 2, 4, 6, 8, 12 and 24 h post- operatively. POST was graded on a four point scale (0-3): 0 = no sore throat; 1 = mild sore throat (complains of sore throat only on asking); 2 = moderate sore throat (complains of sore throat on his/her own); and 3 = severe sore throat (change of voice or hoarseness, associated with throat pain).^[9]

Ramsay sedation score was measured at 1 h after extubation for sedation assessment (1-6): 1= Anxious or restless or both, 2= Cooperative, oriented and tranquil, 3= Responding to commands, 4= Brisk response to stimulus, 5= Sluggish response to stimulus, 6= No response to stimulus.

Statistical Analysis

The sample size was determined by evaluating incidence of post operative sore throat in ketamine and control group which was the primary objective of our study. A pilot study was carried on 12 patients with 6 patients in each group. Main study variable viz. sore throat incidence, Ramsay sedation scale and any side effects were noted in all patients and mean ± SD were calculated. Based on previous literature, the mean effect size (d) of 9 incidence between two groups with a standard deviation of 14 was hypothesized. By using statistical power of 80% and a type 1 alpha error =0.05, with a type 2 error of beta=0.2, sample size of 38 patients per group was calculated. To reduce the probability of dropout, we enrolled total 80 patients (40 in each group). Data were composed, tabulated and then analysed using Statistical Package for the Social Sciences (SPSS) software statistics version 22.0 (IBM corp., Armonk, NY, USA). Continuous parameters were expressed as mean ± SD while categorical parameters were expressed as percentage. With regard to continuous variables, unpaired student's t-

test was used. Chi-square test was used to compare categorical variables. Difference in the incidence of POST between groups was compared with Fisher's exact test or Chi square test whichever was applicable. Results were considered statistically significant if p value < 0.05.

RESULTS

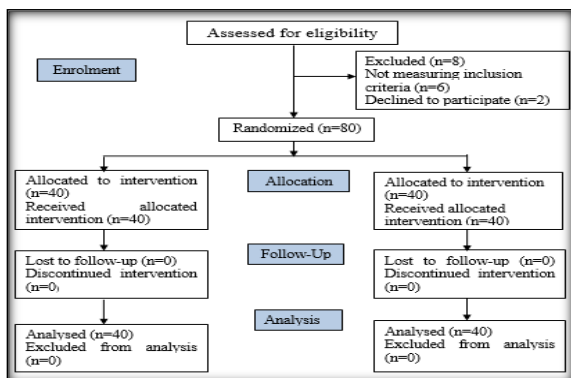


Figure 1: Flow Chart of Study Participants

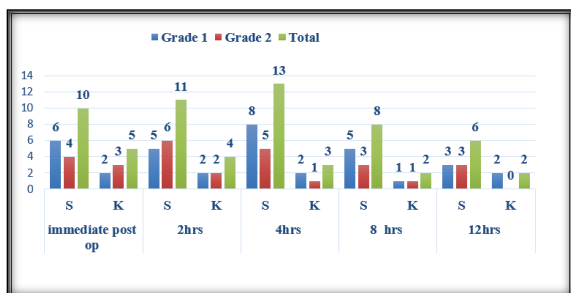


Figure 2: Bar Chart Illustrating Comparison of Incidence and Severity of Sore Throat Among Two Groups

Abbreviations: hrs, hours; S, group S; K, group K; post op, postoperative.

Table 1: Comparison of Demographic Data*

Parameters	Group K (n= 40)	Group S (n= 40)	P value**
Age in years	41.56±12.34	39.32±11.22	0.772
Weight in kg	61.23±12.48	60.86±14.21	0.674
Males (%)	25	28	0.662
Females (%)	15	12	0.561
Duration of surgery (min)	53.44±5.12	54.34±6.71	0.463

Abbreviations: Kg, kilogram; min, minute.

*Data are presented as mean ± standard deviation, number or percentage. **P< 0.05 was considered significant.

Table 2: Comparison of Incidence and Severity of Postoperative Sore Throat between study Groups

Grading of Sore Throat	Number of patients											
	0 h		2 h		4h		8 h		12h		24 h	
	Group S	Group K	Group S	Group K	Group S	Group K	Group S	Group K	Group S	Group K	Group S	Group K
1	6	2	5	2	8	2	5	1	3	2	2	1
2	4	3	6	2	5	1	3	1	3	0	0	0
Total	10	5	11	4	13	3	8	2	6	2	2	1
P value	0.001		0.021		0.002		0.002		0.023		0.049	

Abbreviations: h, hours.

P<0.05 was considered significant

Comparison of incidence and severity of sore throat in two groups were mentioned in Table 2. The

As shown in [Figure 1], we assessed 88 patients for eligibility and randomized 80 patients equally in two study groups. Out of this, 8 patients were not randomized as they either did not meet all eligibility criteria or declined to consent. All patients completed the study and the result were analysed. There were no statistically significant differences regarding age, weight, sex and duration of surgery between two groups. [Table 1]

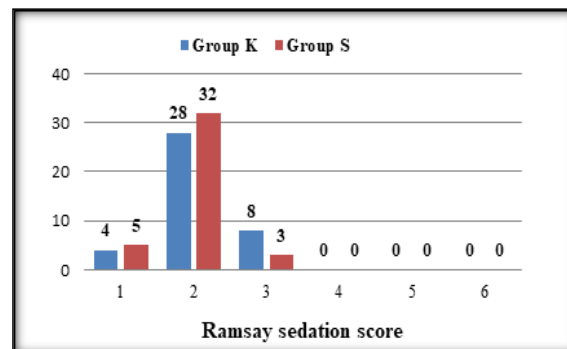


Figure 3: Comparison of Ramsay sedation score at 1 Hour Post Extubation between Study Groups

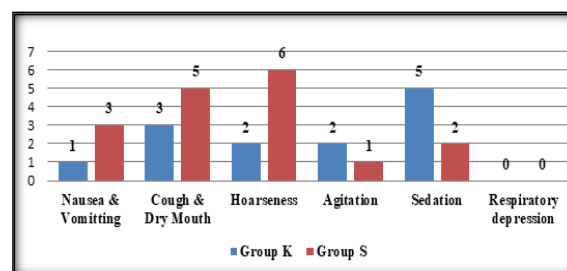


Figure 4: Post Operative Side Effects in Study Groups

overall incidence of POST in the present study was 39%: 7 (18%) patients in group K and 24 (60%)

patients in group S had POST at some point of the study (Fisher's exact $P = 0.01$). Incidence of POST was significantly higher in group S when compared to group K at 2 h and 4 h in post-operative period. [Figure 2]

Primary outcome was to observe sore throat incidence at 2 h and 4 h postoperatively. POST experienced in 11 patients in group S and 4 patient in group K at 2 h postoperatively which was clinically significant ($P = 0.02$). 13 patients in group S versus 3 patients in group K ($P = 0.002$) observed sore throat at 4 h (Table 2). None of the patient in any group had sore throat score > 2 . From above data, it stated that there was statistically significant attenuation of sore throat at 2 h and 4 h in group K compared to group S and effect last up to 24 h in group K.

In [Figure 3], we compared the Ramsay sedation score at 1 h post extubation within two groups. Just after 1 h of extubation, Ramsay sedation score 2 and 3 was higher in the group K than group S, but the difference was statistically non-significant ($P = 0.26$). Sedation score > 4 is not observed in any patient of both groups. In figure 4, we compared side effects among 2 groups. Side effects like vomiting, cough and hoarseness of voice were observed more in the control group (group S) than ketamine group. Sedation (5 cases) and agitation (2 cases) were more often in group K than group S which was statistically non-significant although clinically significant ($P = 0.32$).

DISCUSSION

The present study was to evaluate the role of ketamine nebulization on incidence and severity of POST. In patients receiving ketamine nebulization, we observed reduction in the incidence and severity of sore throat at 2 h and 4 h postoperatively as compared to control group following GA. Ketamine is NMDA receptor antagonist, peripherally administered NMDA receptor antagonists are involved with antinociception and anti-inflammatory cascade. The possible mechanism may be topical effect of ketamine nebulization that attenuates the local inflammation and also has a peripheral analgesic effect is seen for reducing POST.^[8-11] This results is in line with the study done by Chan L who measured intra-operative serum ketamine level and suggested a topical effect of ketamine in attenuation of POST as systemic absorption was unlikely with such low level of serum ketamine.^[12]

We observed an overall incidence of 39% of POST in our patients. Out of this, POST occurred only in 18% of the patients in the ketamine group that was lower as compared to other studies in which the incidence of POST was 21–65%.^[1,2] The primary outcome of the study was the incidence of POST at 2 h and 4 h postoperatively as by this time the patients are generally awake, alert and more

cooperative to participate in the study which is also supported by earlier studies.^[9,12]

Our reasoning of using the nebulized form of ketamine rather than its other forms (oral, IV, gargle) was primarily oriented for safety and ease of administration to the patient in the immediate pre-operative period. Deposition of aerosol in the mouth and upper airway probably reduce POST due to topical analgesic effect of nebulized ketamine.^[13] Amingad B et al compared ketamine nebulization is an effective alternative to ketamine gargle in attenuating sore throat, with no statistical difference between the two. Both the groups showed more than 50% reduction from the reported incidence.^[14]

In present study, group ketamine (K) received ketamine 1mg/kg with 3.0 ml of normal saline nebulisation for 10 min prior to induction to control POST. The study done by M Reddy et al in which 90 patients were randomly allotted in two groups. Group A received 0.5mg/kg, group B received 1mg/kg and Group C received 1.5mg/kg of nebulized ketamine 5 min before intubation. The study concluded that 1mg/kg and 1.5mg/kg dose did not show much difference except increased and thickened secretions in 1.5mg/kg group and 0.5mg/kg dose was comparatively less effective in reducing post-operative sore throat.^[15]

Similarly, studies conducted by Ahuja et al, P. Ramadevi et al,^[16] Archana P et al,^[17] found that nebulized ketamine provide better relief and extended duration of action compared to lignocaine nebulization but lignocaine nebulization is more effective in reducing cough after extubation than ketamine and magnesium sulfate nebulization. Mostafa et al reported that peak incidence of POST was at 2–4 h and incidence of POST at 4 h was significantly less in ketamine group than magnesium sulfate and dexamethasone group.^[18] Magnesium sulfate nebulization reduce sore throat after 4 hour without any change in sedation.^[19] Ranjana et al and Patel N. et al concluded that maximum reduction of POST seen with ketamine followed by magnesium sulfate and then lignocaine nebulization.^[20,21]

In contrast to our study, Mehrotra S et al reported that nebulization with lignocaine was efficacious in reducing cough, ketamine reduced sore throat in early postoperative period whereas long term outcome was better with budesonide.^[22] Based on meta-analysis done by Jian Yu et al, nebulized corticosteroid appeared to be best modality among all and it is a safe alternative to nebulized ketamine.^[23,24]

Although no other studies show the effect of ketamine nebulization on sedation score. Hence, in our study we measured Ramsay sedation score at 1 h postoperatively. We observed that sedation score was higher in group K than group S, but it is clinically non-significant. There are no significant side effects with ketamine nebulization. This result can be supported to the fact that inhaled drug show

very less systemic absorption; so it cause very less systemic side effects.^[18]

There are few limitations to our study, the blood plasma level of ketamine was not measured in our study. We did not measure the incidence of POST beyond 24 hours and laryngoscopy was done by different anaesthetists.

CONCLUSION

The use of ketamine nebulization is well accepted by all patients and effective in reducing the incidence and severity of POST during early recovery period. This technique helps anaesthetist in management of the 'little big problem' of post-operative sore throat.

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