Preoperative ketamine nebulization attenuates the incidence and severity of postoperative sore throat: A randomized controlled clinical trial

ABSTRACT

Background: Endotracheal intubation is the prominent cause of airway mucosal injury which results in postoperative sore throat (POST), with an incidence of 21%–65%. Although this complication is minor, if left unresolved, it produces significant agony and annoyance to the patient. This study was conducted to evaluate the efficacy of nebulized ketamine in decreasing POST.

Materials and Methods: After written informed consent, 96 patients of the American Society of Anesthesiologists physical status (PS) 1–2 between 18 and 60 years, of either sex undergoing general anesthesia (GA) with tracheal intubation were enrolled in this prospective, randomized, placebo-control, and double-blind controlled trial. Patients were randomized into two groups; Group 1 received ketamine 50 mg (1.0 ml) with 4.0 ml of saline nebulization, while Group 2 received saline nebulization 5.0 ml for 15 min. GA was administered 15 min after completing nebulization. On reaching postanesthesia care unit, POST monitoring was done at 0, 2, 4, 6, 12, and 24 h after extubation. POST was graded on a four-point scale (0–3).

Results: The overall incidence of POST in this study was 25%; POST was experienced by 7 patients (14.6%) in ketamine and 17 patients (35.4%) in saline group (Fisher’s exact \( P = 0.018 \)). There was statistically significant reduction in the incidence of POST in ketamine group when compared to saline, at 2, 4, 6, 12, and 24 h postoperatively (\( P < 0.05 \)). Severity of sore throat was also higher in saline group when compared to ketamine at 4 h (\( P = 0.030 \)) and 6 h (\( P = 0.016 \)) postextubation.

Conclusion: Preoperative ketamine nebulization effectively reduced the incidence and severity of POST, with no adverse effects.

Key words: General anesthesia; intubation; ketamine; nebulization; sore throat

Introduction

Postoperative sore throat (POST) is a usual complaint after endotracheal intubation, resulting in significant anguish and annoyance to the patient, with incidence varying from 21 to 65%.[1,2] Eventhough a minor complication, it brings not only agony to the patient but it also makes them feel disappointed with the quality of recovery from anesthesia.
receptor antagonist, has been used for decreasing POST because of its anti-nociceptive and anti-inflammatory action, as gargle as well as in nebulized form.[10‑12] However, nebulized ketamine is better tolerated in patients due to many reasons such as: It saves the patient from the bitter taste of ketamine, also much lesser volume is needed as against larger volumes required for gargle.[12]

This study was undertaken to evaluate the effectiveness of nebulized ketamine in alleviating POST in our population.

**Materials and Methods**

After obtaining the approval of the hospital scientific and ethics committee and informed written consent, 96 patients, in the age group of 18–60 years, with the American Society of Anesthesiologists (ASA) physical status (PS) 1–2, who were scheduled to undergo elective surgical procedures in supine position under general anesthesia (GA) with endotracheal intubation, lasting up to 2 h, were enrolled in this prospective, double-blind, randomized, placebo-controlled study. Exclusion criteria were patients with a history of preoperative sore throat, upper respiratory tract infection, chronic obstructive pulmonary disease, known allergy to study drug, pregnancy, Mallampati Grade >2, undergoing oral, nasal, head-and-neck surgeries, those required more than one attempt at intubation.

Using a computer-generated randomization technique, opaque sealed sequentially numbered envelopes were prepared by an anesthesiologist who was not part of the study, by which patients were randomized into two groups. After opening the envelopes, anesthesia assistant prepared the nebulization solution according to group allocation. The anesthesia assistant who prepared the study drugs did not participate in the subsequent assessment of these patients. Patients were blinded as both the preparations were colorless and tasteless.

The patients recruited for the study were kept fasted for 6 h preceding surgery. On arrival at the operating room, patients were monitored by electrocardiogram, noninvasive blood pressure and pulse oximetry (SpO₂). Anesthesia protocol was made uniform for all patients. The enlisted 96 patients were randomly allocated into two groups of 48 each: Group 1 received ketamine 50 mg (1 ml) with saline (4 ml) nebulization and Group 2 received saline nebulization (5 ml), given through nebulization mask connected to wall-mounted oxygen driven source (8 L, 50 psi) for 15 min (min). GA was induced 15 min after completing nebulization, with intravenous (IV) fentanyl 2 mcg/kg and IV propofol 2 mg/kg. To ensure less trauma, 3 min after administering IV vecuronium bromide 0.1 mg/kg, a brisk and a gentle laryngoscopy lasting <15 s, was done by an experienced anesthesiologist using a Macintosh laryngoscope blade (size 3 or 4). Trachea was then intubated with a sterile single-lumen cuffed polyvinyl chloride tracheal tube with an internal diameter of 7–7.5 mm for women and 8–8.5 mm for men. Tracheal tube cuff was inflated with a volume of room air until no air leakage was audible.

GA was maintained with oxygen 33% in nitrous oxide and sevoflurane. Analgesia during surgery was supplemented with paracetamol 1 g IV, thereafter 6th hourly in the postoperative period. IV ondansetron 4 mg was administered 30 min before the end of surgery and then 8th hourly in the postoperative period. At the end of surgery, the oropharynx was suctioned with care, using a soft disposable suction catheter and neuromuscular block was reversed with IV neostigmine 50 mcg/kg and glycopyrrolate 10 mcg/kg. The endotracheal tube was removed when the patient regained complete consciousness.

After shifting the patient to postanesthesia care unit (PACU), sore throat was assessed by the staff nurse in PACU, who was unaware of the group allocation of the patient, at 0, 2, 4, 6, 12, and 24 h postoperatively, from the time of extubation. POST was graded on a four-point scale (0–3):[11] 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). Even after 24 h, if patients still had moderate or severe sore throat, lukewarm saline gargle and decongestants were prescribed for them. Moreover, if the symptoms still persisted, they were referred for oto-rhino-laryngology consultation. Side effects if any were noted 8th hourly during the first 24 h after extubation.

The primary outcome of our study was to assess how effective ketamine nebulization was, in alleviating POST in adult patients undergoing GA of up to 2 h duration and also to evaluate the incidence and severity POST in those patients. While the secondary outcomes were the evaluation of side effects such as postoperative nausea and vomiting, cough, dry mouth, hallucinations, respiratory depression, and hemodynamic instability in both the groups.

The sample size was calculated from the study,[12] with incidence of POST in Group S as 46% and Group K as 20%. With 95% confidence level and power of study at 80%, the minimum sample size required was found to be 48 in each group. The statistical calculations were performed using the
In this study, the overall incidence of POST was 25%: Seven patients (14.6%) in Group 1 (ketamine), and 17 patients (35.4%) in Group 2 (saline) developed POST at some point of the study (Fisher’s exact \( P = 0.018 \)). Incidence of POST was significantly lower in Group 1 when compared to Group 2 at 2, 4, 6, 12, and 24 h postoperatively [Figure 2].

At 2 h postextubation, 16 patients in Group 2 versus 6 patients in Group 1 (ketamine) \( (P = 0.015^* \) experienced postoperative sore throat. In saline group, 17 patients developed POST versus six patients in ketamine group \( (P = 0.009^* \) at 4 h, which was statistically significant. Similar statistically significant observations were found at 6 h, postoperatively. In addition, incidence of POST was found to be higher in saline group when compared to

Table 1: Patient characteristics

| Characteristics          | Group 1 (ketamine) | Group 2 (saline) | \( P \) |
|--------------------------|-------------------|------------------|------|
| Age (years)              | 38.94 (14.58)     | 35.17 (13.41)    | 0.190|
| Weight (kg)              | 63.67 (8.45)      | 66.29 (7.93)     | 0.110|
| Duration of surgery (min)| 87.29 (18.62)     | 92.88 (15.6)     | 0.108|
| Male/female              | 22/26             | 22/26            | 1.00 |
| ASA PS (Grade 1/2)       | 29/19             | 31/17            | 0.673|

Data expressed as mean (SD) or n. SD: Standard deviation; PS: Physical status; ASA: American Society of Anesthesiologists
ketamine group at 12 h ($P = 0.036^*$) and 24 h ($P = 0.049^*$), from the time of extubation [Table 2].

While comparing the severity of POST, a higher incidence of Grade 2 (moderate) sore throat was observed in saline group when compared to ketamine group at 4 h ($P = 0.030^*$) and 6 h ($P = 0.016^*$) postoperatively which was statistically significant [Table 3]. None of the patients had severe sore throat (Grade 3) in both groups. No adverse effects such as nausea, vomiting, cough, stridor, laryngospasm, dry mouth, hoarseness, hallucinations, respiratory depression, or hemodynamic instability were noticed throughout observation.

**Discussion**

POST is a frequent complaint after endotracheal intubation, which results in significant patient discomfort and disappointment with the quality of care. Several trials had been done recently with ketamine, an NMDA-receptor antagonist, in various routes such as gargle, nebulization as well as IV, in reducing POST with conflicting results.[10-15] The present study was designed to determine the effectiveness of nebulized ketamine in attenuating POST, following GA with tracheal intubation, lasting up to 2 h.

Several factors have been identified in earlier studies contributing to sore throat after surgery, including patient age, sex, cuff design, intracuff pressure, and tracheal tube size.[16-18] In our study, both groups were comparable in distribution of age, gender, body weight, ASA PS, and duration of surgery, and hence, no correlation with sore throat was noted.

In previous studies, the incidence of POST was 21%–65%.[1,2] However, in our study, we noted an overall incidence of 25% and out of this, 35.4% in the saline group experienced POST.

![Figure 2: Incidence of postoperative sore throat. Number of patients on Y axis hours after extubation on X axis. *P < 0.05 in between group comparison considered statistically significant](image)

| Time period | Sore throat incidence | Group 1 (ketamine) | Group 2 (saline) | P   |
|-------------|-----------------------|-------------------|-----------------|-----|
| 0 h         | Absent                | 41                | 33              | 0.052 |
|             | Present               | 7                 | 15              |     |
| 2 h*        | Absent                | 42                | 32              | 0.015* |
|             | Present               | 6                 | 16              |     |
| 4 h*        | Absent                | 42                | 31              | 0.009* |
|             | Present               | 6                 | 17              |     |
| 6 h*        | Absent                | 42                | 31              | 0.009* |
|             | Present               | 6                 | 17              |     |
| 12 h*       | Absent                | 43                | 35              | 0.036* |
|             | Present               | 5                 | 13              |     |
| 24 h*       | Absent                | 44                | 35              | 0.049* |
|             | Present               | 4                 | 11              |     |

*Significant at the 0.05 level

**Table 2: Incidence of postoperative sore throat**

| Time period | Sore throat grade | Group 1 (ketamine) | Group 2 (saline) | P   |
|-------------|-------------------|-------------------|-----------------|-----|
| 0 h         | 0                 | 41                | 33              | 0.123 |
|             | 1                 | 7                 | 14              |     |
|             | 2                 | 0                 | 1               |     |
| 2 h         | 0                 | 42                | 32              | 0.051 |
|             | 1                 | 5                 | 14              |     |
|             | 2                 | 1                 | 2               |     |
| 4 h         | 0                 | 42                | 31              | 0.030* |
|             | 1                 | 5                 | 13              |     |
|             | 2                 | 1                 | 4               |     |
| 6 h         | 0                 | 42                | 31              | 0.016* |
|             | 1                 | 6                 | 13              |     |
|             | 2                 | 0                 | 4               |     |
| 12 h        | 0                 | 43                | 35              | 0.079 |
|             | 1                 | 5                 | 11              |     |
|             | 2                 | 0                 | 2               |     |
| 24 h        | 0                 | 44                | 37              | 0.124 |
|             | 1                 | 4                 | 10              |     |
|             | 2                 | 0                 | 1               |     |

*Significant at the 0.05 level

While only 14.6% of the patients developed POST in the ketamine group, which was much lower when compared to earlier studies. In the present study, there was significant decline in the incidence of POST at 2 , 4 , 6 , 12, and 24 h while reduction in the severity of POST in the ketamine group was observed at 4 h and 6 h, postextubation. POST is probably caused by injury to the pharyngeal mucosa during laryngoscopy, resulting in an aseptic inflammatory process or irritation to the tracheal mucosa produced by endotracheal tube cuff or it can also be due to injury to tissues during intubation and extubation.[7,10,19] Chan et al., in his study using ketamine gargle for reducing POST,[20] measured intraoperative serum ketamine levels. They demonstrated low serum levels of ketamine and suggested a topical action of ketamine resulted in the attenuation of POST rather than a systemic effect. Hence, the significant reduction in the
incidence and severity of postoperative sore throat in our study can be attributed to the topical effect of ketamine nebulization, by its NMDA-antagonistic and anti-inflammatory action, which relieved the local inflammation and produced peripheral analgesia.\cite{5,8,11,21,24}

In a study done by Ahuja et al.,\cite{12} they observed a decrease in the incidence of POST in ketamine group, which was statistically significant only at 2 h and 4 h postoperatively and concluded that ketamine nebulization when given preoperatively lessened the incidence and severity of POST, particularly during the initial hours of postoperative period. However, in the present study, we noticed that the incidence of POST in ketamine group showed a statistically significant decrease at 2, 4, 6, 12, and 24 h, postextubation. In an experimental animal study, ketamine nebulization was reported to have a shielding effect on airway inflammation.\cite{24} It was also shown that the usual anti-inflammatory processes which was triggered following an injury, was prevented by ketamine to excessively overpower the pro-inflammatory influences.\cite{25} In another study, with 3.0 ml (225 mg) of isotonic magnesium sulfate which is also a NMDA-receptor antagonist, when given preoperatively, revealed an attenuation in the incidence and severity of POST at 0, 2, 4, and 24 h postoperatively.\cite{26} Hence, a prophylactic use of nebulized ketamine could prevent airway inflammation and cause peripheral analgesia, which might be responsible for the significant decline in the incidence and severity of sore throat in this study, during the first postoperative day.

Our inclusion and exclusion criteria were well-defined and tracheal intubation was performed by experienced anesthesiologists. We used nebulized form of ketamine in this study instead of its other forms such as oral, IV or gargle, mainly due to the fact that, it was safe and more easy to administer to the patient, especially at a time immediately before surgery. For this, we used a wall-mounted oxygen driven nebulization method. In this method, liquid is broken up into droplets by the compressed air. Largest droplets are filtered within the nebulizer, but larger particles (10–25 μm) mostly deposit in mouth and throat and those of 5–10 μm diameter get deposited in a passage from mouth to airway.\cite{27} This settling of aerosol in mouth and upper airway might probably be the reason for the decreased incidence and severity of POST in ketamine group, due to its topical analgesic, anti-inflammatory, and NMDA-receptor antagonistic effect.

There are a few limitations of our study. Cuff pressure monitoring was not done during anesthesia, and no formal sedation scale was used. We were also not able to measure plasma ketamine levels during the period of study and follow-up was not extended beyond 24 h. Moreover, further studies are needed, comparing the efficacy between ketamine gargle and ketamine nebulization, also the time of administration of nebulization – before or after surgery.

**Conclusion**

Preoperative administration of nebulized ketamine effectively attenuated the incidence and severity of POST in patients undergoing GA with endotracheal intubation, with no adverse effects.

**Acknowledgment**

We thank Mr. Kevin Suresh, who conducted the statistical analysis of the data of our study. We also express our sincere gratitude to all the patients who participated in the study and to the staff of Department of Anaesthesiology.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Higgins PP, Chung F, Mezei G. Postoperative sore throat after ambulatory surgery. Br J Anaesth 2002;88:582-4.
2. Loeser EA, Bennett GM, Orr DL, Stanley TH. Reduction of postoperative sore throat with new endotracheal tube cuffs. Anesthesiology 1980;52:257-9.
3. el Hakim M. Beclomethasone prevents postoperative sore throat. Acta Anaesthesiol Scand 1993;37:250-2.
4. Thomas S, Beevi S. Dexamethasone reduces the severity of postoperative sore throat. Can J Anaesth 2007;54:897-901.
5. Bagchi D, Mandal MC, Das S, Sahoo T, Basu SR, Sarkar S, et al. Efficacy of intravenous dexamethasone to reduce incidence of postoperative sore throat: A prospective randomized controlled trial. J Anaesthesiol Clin Pharmacol 2012;28:477-80.
6. Ogata J, Minami K, Horishita T, Shiraiishi M, Okamoto T, Terada T, et al. Gargling with sodium azulene sulfonate reduces the postoperative sore throat: A prospective randomized controlled trial. J Anaesthesiol Clin Pharmacol 2012;28:477-80.
7. Huang YS, Hung NK, Lee MS, Kuo CP, Yu JC, Huang GS, et al. The effectiveness of benzylamine hydrochloride spraying on the endotracheal tube cuff or oral mucosa for postoperative sore throat. Anesth Analg 2010;111:887-91.
8. Zhu MM, Zhou QH, Zhu MH, Rong HB, Xu YM, Qian YN, et al. Effects of nebulized ketamine on allergen-induced airway hyperresponsiveness and inflammation in actively sensitized Brown-Norway rats. J Inflamm (Lond) 2007;4:10.
9. Davidson EM, Carlton SM. Intraplantar injection of dextrorphan, ketamine or memantine attenuates formalin-induced behaviors. Brain Res 1998;785:136-42.
10. Rudra A, Ray S, Chatterjee S, Ahmed A, Ghosh S. Gargling with ketamine attenuates the postoperative sore throat. Indian J Anaesth 2009;53:40-3.
11. Canbay O, Celebi N, Sahin A, Celiker V, Ozgen S, Aypar U, et al.
Thomas, et al.: Preoperative ketamine nebulization attenuates postoperative sore throat. Br J Anaesth 2008;100:490-3.
12. Ahuja V, Mitra S, Sarna R. Nebulized ketamine decreases incidence and severity of post-operative sore throat. Indian J Anaesth 2015;59:37-42.
13. Teymourian H, Mohajerani SA, Farahbod A. Magnesium and ketamine gargle and postoperative sore throat. Anesth Pain Med 2015;5:e22367.
14. Park SY, Kim SH, Noh JI, Lee SM, Kim MG, Kim SH, et al. The effect of intravenous low dose ketamine for reducing postoperative sore throat. Korean J Anesthesiol 2010;59:22-6.
15. Jain S, Bendwal H, Gohiya S, Alwani N, Pancholi S, Romday R. Comparison of nebulized ketamine and ketamine with clonidine in postoperative sore throat. Int Surg J 2017;4:1579-83.
16. Rudra A, Roy S. Comparative study with the different types of endotracheal tubes, cuffs, intra-cuff pressure on the postoperative sore throat. Calcutta Med J 1985;82:66-9.
17. Stenqvist O, Nilsson K. Postoperative sore throat related to tracheal tube cuff design. Can Anaesth Soc J 1982;29:384-6.
18. Mandøe H, Nikolajsen L, Lintrup U, Jepsen D, Molgaard J. Sore throat after endotracheal intubation. Anesth Analg 1992;74:897-900.
19. Park SH, Han SH, Do SH, Kim JW, Rhee KY, Kim JH, et al. Prophylactic dexamethasone decreases the incidence of sore throat and hoarseness after tracheal extubation with a double-lumen endobronchial tube. Anesth Analg 2008;107:1814-8.
20. Chan L, Lee ML, Lo YL. Postoperative sore throat and ketamine gargle. Br J Anaesth 2010;105:97.
21. Khatavkar SS, Bakhshi RG. Comparison of nasal midazolam with ketamine versus nasal midazolam as a premedication in children. Saudi J Anaesth 2014;8:17-21.
22. Damle SG, Gandhi M, Laheri V. Comparison of oral ketamine and oral midazolam as sedative agents in pediatric dentistry. J Indian Soc Pedod Prev Dent 2008;26:97-101.
23. Hirota K, Lambert DG. Ketamine: New uses for an old drug? Br J Anaesth 2011;107:123-6.
24. Zhu MM, Qian YN, Zhu W, Xu YM, Rong HB, Ding ZN, et al. Protective effects of ketamine on allergen-induced airway inflammatory injury and high airway reactivity in asthma: Experiment with rats. Zhonghua Yi Xue Za Zhi 2007;87:1308-13.
25. De Kock M, Loix S, Lavand’homme P. Ketamine and peripheral inflammation. CNS Neurosci Ther 2013;19:403-10.
26. Gupta SK, Tharwani S, Singh DK, Yadav G. Nebulized magnesium for prevention of postoperative sore throat. Br J Anaesth 2012;108:168-9.
27. O’Callaghan C, Barry PW. The science of nebulised drug delivery. Thorax 1997;52 Suppl 2:S31-44.