

# 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; sorethroat

## 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%.<sup>[1,2]</sup> 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.

Various nonpharmacological and pharmacological methods had been studied extensively for decreasing POST with varying results.<sup>[3-7]</sup>

It is noted that N-methyl-d-aspartate (NMDA) has a role in nociception and inflammation.<sup>[8,9]</sup> Ketamine, an NMDA

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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.<sup>[10-12]</sup> 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.<sup>[12]</sup>

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 (SpO<sub>2</sub>). 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 6<sup>th</sup> hourly in the postoperative period. IV ondansetron 4 mg was administered 30 min before the end of surgery and then 8<sup>th</sup> 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), sorethroat 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):<sup>[11]</sup> 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 8<sup>th</sup> 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,<sup>[12]</sup> 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

software Statistical Package for the Social Sciences (SPSS) for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). The following statistical methods were employed in the present study. Differences in the age, weight, and duration of surgery were done using student *t*-test. ASA grading and differences in the incidence of POST were analyzed using Fisher's exact *t*-test or Chi-square test. The level of significance was set at 0.05 and all tests were two sided.

### Results

We screened 107 patients for this prospective, double-blind, randomized, and placebo-controlled trial. As the inclusion criteria were not fulfilled, we excluded eleven patients from our study; four patients had ASA PS Grade >2, three patients had Mallampati Grade >2, two patients had preoperative sore throat, one patient had asthma, and one patient was undergoing nasal surgery. Hence, a total of 96 patients were recruited and allocated into two groups of 48 each. All these patients finished the study and were available for follow-up and data collection [Figure 1]. Both groups were comparable in distribution of age, gender, body weight, ASA PS, and duration of surgery [Table 1]. Surgeries in both the groups included fibroadenoma breast, abdominal, urological, and orthopedic procedures.

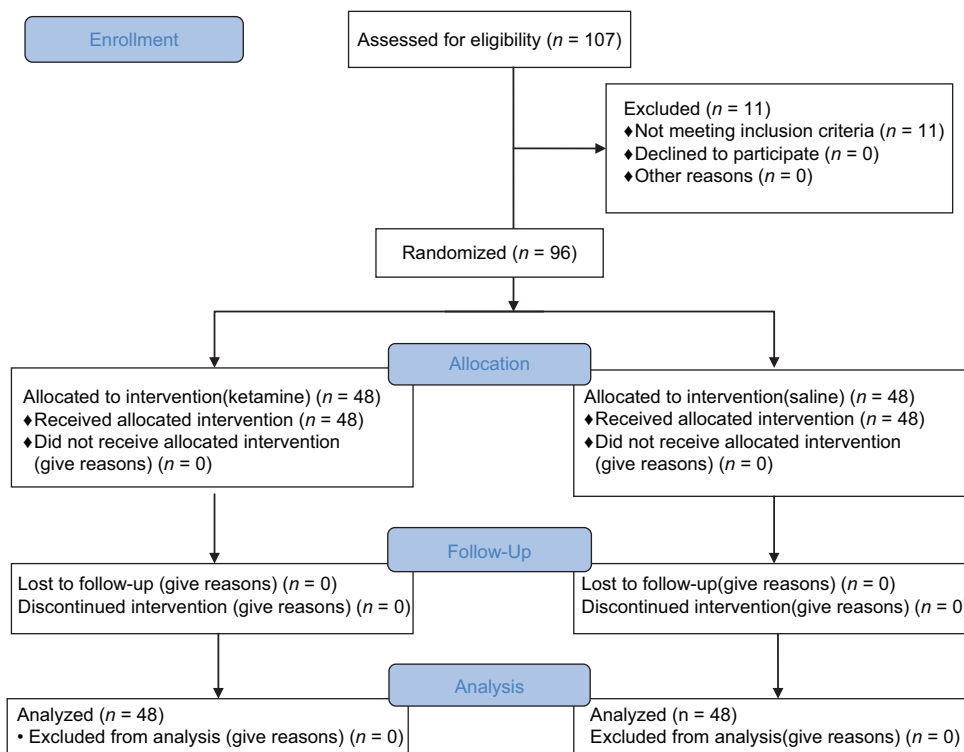
In this study, the overall incidence of POST was 25%: Seven patients (14.6%) in Group 1 (ketamine), and 17 patients (35.4%) in Group 2 (saline) developed POST at some point of the study (Fisher's exact *P* = 0.018). Incidence of POST was significantly lower in Group 1 when compared to Group 2 at 2, 4, 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

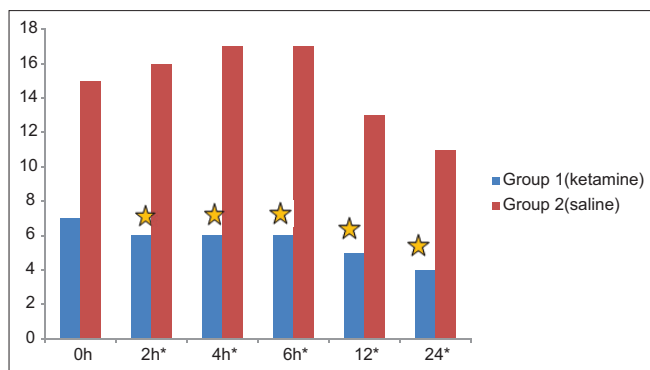
**Table 1: Patient characteristics**

Characteristics	Group 1 (ketamine)	Group 2 (saline)	<i>P</i>
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



**Figure 1: CONSORT flow diagram**



**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**

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 sorethroat (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.<sup>[10-15]</sup> 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.<sup>[16-18]</sup> 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%.<sup>[11,2]</sup> However, in our study, we noted an overall incidence of 25% and out of this, 35.4% in the saline group experienced POST.

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

Time period	Sore throat incidence	Group 1	Group 2	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	37	0.049*
	Present	4	11	

\*Significant at the 0.05 level

**Table 3: Severity of postoperative sore throat in patients**

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.<sup>[7,10,19]</sup> Chan *et al.*, in his study using ketamine gargle for reducing POST,<sup>[20]</sup> 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 sorethroat 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.<sup>[8,11,21-24]</sup>

In a study done by Ahuja *et al.*,<sup>[12]</sup> 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.<sup>[24]</sup> It was also shown that the usual antipro-inflammatory processes which was triggered following an injury, was prevented by ketamine to excessively overpower the pro-inflammatory influences.<sup>[25]</sup> 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.<sup>[26]</sup> 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 sorethroat 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.<sup>[27]</sup> 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.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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