Clinical Investigation

Nebulized ketamine decreases incidence and severity of post-operative sore throat

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ABSTRACT

Background and Aims: Post-operative sore throat (POST) occurs in 21–65% of patients. Ketamine used earlier as gargle for reducing POST has limitations. The aim of this study was to see if nebulised ketamine reduces POST. **Methods:** We conducted a prospective, randomised, placebo-control, and double-blind controlled trial. After written informed consent, 100 patients belonging to American Society of Anaesthesiologists physical status I–II in the age group 20–60 years, of either sex undergoing surgery under general anaesthesia (GA) were enrolled. Patients were randomised into two groups; group saline (S) received saline nebulisation 5.0 ml and group ketamine (K) received ketamine 50 mg (1.0 ml) with 4.0 ml of saline nebulisation for 15 min. GA was induced 10 min after completion of nebulisation in the patients. The POST and haemodynamic monitoring were done pre-nebulization, pre-induction, on reaching post-anaesthesia care unit, and at 2, 4, 6, 8, 12 and 24 h post-operatively. POST was graded on a four-point scale (0–3). **Results:** The overall incidence of POST was 33%; 23 patients (46%) in saline and 10 patients (20%) in ketamine group experienced POST (Fisher's exact $P = 0.01$). The use of 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 4 patients in group K ($P = 0.03$) experienced POST at 4 h. The moderate sore throat occurred in 6 patients in group S and none in group K at 2 h, post-operatively ($P = 0.02$). **Conclusion:** Ketamine nebulization significantly attenuated the incidence and severity of POST, especially in the early post-operative period, with no adverse effects.

Key words: Ketamine, nebulization, post-operative sore throat, tracheal intubation

INTRODUCTION

Post-operative sore throat (POST) occurs in 21–65% of patients receiving general anaesthesia (GA) with tracheal intubation.[1,2] Though considered as a minor complication, but it may cause significant post-operative morbidity and patient dissatisfaction.[3] Various non-pharmacological and pharmacological trials have been used for attenuating POST with no proven single modality.

The pharmacological methods used to reduce POST include use of beclomethasone gel, gargling with azulene sulphonate, ketamine and licorice.[4-6] Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist and has been used as a gargle for reducing the incidence and severity of POST due to its anti-nociceptive and anti-inflammatory effects.[6,7] Ketamine nebulization has a few advantages over gargle: It spares the patient from the bitter taste of ketamine, much smaller volume is required as opposed to larger volumes required for gargle with risk of aspiration if accidentally swallowed; hence better patient cooperation is likely. So far no study has been conducted to evaluate efficacy of nebulized ketamine for prevention of POST.

The main objective of this study was to evaluate the role of nebulized ketamine for attenuation of POST in patients undergoing surgeries under GA with tracheal intubation.

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METHODS

The present study was conducted after receiving approval by the Institute Ethics Committee of our hospital and written informed consent from 100 patients belonging to ASA physical status I–II, in the age group of 20 and 60 years, of either sex, undergoing surgery in supine position under GA lasting for up to 1 h. Patients with a history of pre-operative sore throat, oral surgeries, asthma, chronic obstructive pulmonary disease, head and neck surgeries, Mallampati grade >2, known allergies to study drug, recent non-steroidal anti-inflammatory drug medication, and those who required more than one attempt at intubation were excluded from the study. A pilot study carried out in ten patients revealed that nebulised ketamine (Aneket® 50 mg/ml ampoule 2 ml, Neon Laboratories Ltd., Mumbai, India, active ingredient ketamine, preservative free) was tasteless.

Patients were enrolled a day prior to surgery by investigators in the surgical ward. Patients were randomised into two groups with the help of computer-generated random number tables in opaque sealed envelopes prepared by an anaesthesiologist not part of the study. The envelopes were opened by the staff nurse, and nebulisation solution was prepared according to group allocation. Group saline (S) received a saline nebulisation 5.0 ml and group ketamine (K) received ketamine 50 mg (1.0 ml) (with 4.0 ml of the saline) nebulisation. The preparations of 5.0 ml each were administered by the staff nurse. The patients received the study drug via nebulisation mask connected to wall-mounted oxygen driven source (8 L, 50 psi) for 15 min. The staff nurse later did not participate in the subsequent assessment of these patients. Patients were blinded as both the preparations were tasteless. GA was induced 10 min after completion of nebulization in the patients. The intra-operative monitoring included continuous electrocardiography, non-invasive blood pressure, pulse oximetry (SpO_2), and end-tidal carbon dioxide. GA was induced with intravenous (IV) morphine100 μg/kg and propofol 2 mg/kg. Tracheal intubation was facilitated with IV vecuronium bromide 0.1 mg/kg, IV lignocaine 1 mg/kg and the trachea was intubated with a soft seal cuffed sterile polyvinyl chloride tracheal tube (Portex®, Smith Medical, Hansraj Nayyar Medical, Mumbai, Maharashtra, India) with an internal diameter of 7–7.5 mm for women and 8–8.5 mm for men. Tracheal intubation was performed by an experienced anaesthesiologist after ensuring maximum neuromuscular blocking effect as assessed by train of four (TOF) count <2. GA was maintained with oxygen 33% in nitrous oxide and supplemented with isoflurane. IV ondansetron 4 mg was administered 30 min prior to end of surgery and then 8 h in the post-operative period. IV dexamethasone 8 mg as a single dose was given as rescue antiemetic. The tracheal tube cuff was inflated until no air leakage could be heard with a stethoscope at peak airway pressure of 20 cm H_2O. At the completion of surgery, with the patient adequately anesthetised, the oropharynx was gently suctioned, and the isoflurane was then turned off. Inspiratory oxygen concentration was increased to 100%. The neuromuscular block was reversed with IV neostigmine 50 μg/kg and glycopyrrolate 10 μg/kg while awaiting the return of spontaneous ventilation. During extubation, if a patient had excessive coughing, IV lignocaine 1.5 mg/kg was administered as a rescue measure. Trachea was extubated at T4/T1 ratio of > 90% and the patient fully conscious.

Sore throat assessment, and haemodynamic recording were done at pre-nebulisation (baseline parameters before nebulisation of patient), pre-induction (parameters after nebulization and just before induction of GA), immediate recovery (0 h), 2, 4, 6, 8, 12 and 24 h post-operatively. POST was graded on a four-point scale (0–3):[6] 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). Other side-effects, if any, were noted. IV paracetamol 1 gm 6th hrly and diclofenac 100 mg suppository twice daily were used for post-operative pain relief.

The primary outcome of the study was to measure the incidence of POST at 4 h post-operatively in adult patients undergoing surgery of duration of up to 1 h under GA. The secondary outcomes included the incidence and severity of POST at immediate recovery, and post-operatively, evaluation of side-effects including nausea, vomiting, cough and dry mouth in both the groups.

Calculation of sample size was based on the assumption that the incidence of POST is 65% and to show a 50% reduction in the incidence at α =0.05, confidence interval of 95% and a power 90% we required a sample size of 46 patients per group. On adding 10% patients for possible loss to follow-up, the sample size required was 50 patients per group. The collected

data were analysed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA, version 15.0 for windows). Kolmogorov–Smirnov Test was used to see normality of age, weight and haemodynamics and differences in the age and weight were done using an independent *t*-test. Haemodynamic variables between the groups were compared with *t*-test and within the group over time were compared using analysis of variance. Differences in the incidence of POST among the groups were compared with Fisher's exact test or Chi-square test whichever was applicable. Groups were compared with Mann–Whitney U-test for severity of POST. All tests were two-sided. $P < 0.05$ was considered as statistically significant.

RESULTS

We screened 108 patients for this prospective, randomized and placebo-controlled trial. Out of these eight patients were excluded as they did not fulfil the inclusion criteria; three patients had pre-operative sore throat, two patients were scheduled for oral surgery, one patient had asthma and two patients had Mallampati grade > 2. Hence, a total of 100 patients were enrolled and randomized into two groups of 50 patients each. All the patients completed the study, and the results were analysed [Figure 1]. There were no significant differences between the two groups regarding age, body weight, gender distribution, ASA grade or duration of surgery [Table 1]. Surgeries in both the groups included abdominal surgeries, fibroadenoma breast, incision hernia, and restoration of bowel continuity.

The overall incidence of POST in the present study was 33%: 23 (46%) patients in group S and 10 (20%) patients in group K 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 post-operatively [Figure 2].

The primary outcome was to observe the incidence of POST at 4 h, post-operatively. POST occurred in 13 patients in group S versus 4 patients in group K ($P = 0.03$), which was significant. 13 patients in group S versus 3 patients in group K ($P = 0.01$) experienced POST at 2 h post-operatively [Figure 2]. Patients who experienced POST were compared for severity of POST. POST was significantly attenuated at 2 h in group K compared to group S; 6 patients in

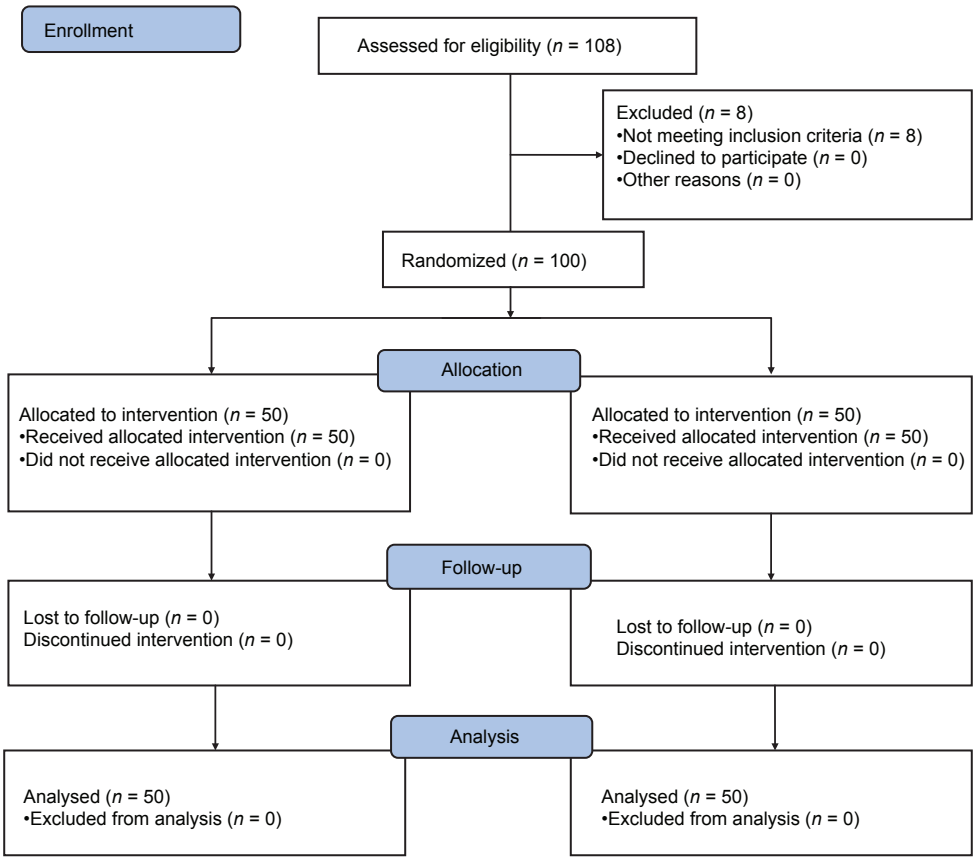

Figure 1: Consolidated Standards of Reporting Trials flow diagram. Group S – Saline group; Group K – Ketamine group

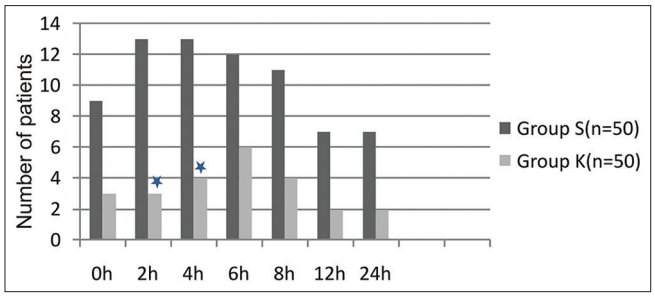

Figure 2: Incidence of post-operative sore throat at 0, 2, 4, 6, 8, 12 and 24 h post-operatively in both the groups. *P < 0.05 in between group comparison considered statistically significant. Group S – Saline group; Group K – Ketamine group

group S and none in group K experienced POST score 2 ($P = 0.02$) [Table 2]. During extubation of the trachea, none of the patients required rescue IV lignocaine.

Patients in both the groups remained haemodynamically stable with no nausea, vomiting, stridor, laryngospasm, cough, dry mouth, hoarseness, dissociative symptoms or any other adverse effect during the entire study period.

DISCUSSION

The present study is the first to evaluate the role of ketamine nebulisation on incidence and severity of POST. We observed reduction in the incidence at 2 h and 4 h, and attenuation of severity of POST at 2 h, in patients receiving ketamine nebulisation as compared to control group, following GA with tracheal intubation lasting for up to 1 h. The incidence of POST was 21–65% in earlier studies.[1,2] but we observed an overall incidence of 33% of POST in our patients. Out of this POST occurred only in 20% of the patients in the ketamine group that was lower as compared to other studies.

In the present study, the incidence of POST at 2 and 4 h was significantly reduced, and the attenuation of severity of POST occurred in the ketamine group at 2 h. The mechanism of effect was possibly the topical effect of ketamine nebulization that attenuated the local inflammation and also due to peripheral analgesic effect of ketamine.[6-9] Literature supports the topical effect of ketamine via its NMDA-antagonistic action and anti-inflammatory effect based on animal model data.[7-11] Ketamine is an NMDA receptor antagonist with the primary site of action in the central nervous system, and parts of the limbic system while its use via nasal route, gargle, and rectal route suggests its peripheral effect.[6-9] Experimental animal studies have

Table 1: Demographic data

Characteristics	Group S (*n*=50)	Group K (*n*=50)
Age (years)	42.6 (15.1)	40.1 (13.2)
Weight (kg)	60 (9.7)	60 (13.1)
Male (%)	36 (72)	30 (60)
Duration of surgery (min)	54 (5)	55 (6)

Data expressed as mean (standard deviation) or numbers (%)

Table 2: Severity of POST in patients

Time	POST score	Group S (*n*=50)	Group K (*n*=50)
Immediate recovery (0 h)	1	7	3
	2	2	0
2 h	1	7	3
	2	6	0*
4 h	1	8	3
	2	5	1
6 h	1	9	5
	2	3	1
8 h	1	10	4
	2	1	0
12 h	1	5	2
	2	2	0
24 h	1	5	2
	2	2	0

Data expressed as number of patients. *P<0.05 on between group comparison considered statistically significant. POST – Post-operative sore throat

shown a protective effect on airway inflammatory injury with ketamine nebulisation.[11] In an earlier study, pre-operative nebulisation with 3.0 ml (225 mg) of isotonic magnesium sulphate, also a NMDA receptor antagonist showed a decrease in incidence and severity of POST at 0, 2, 4 and 24 h post-operatively.[12]

The primary outcome of the study was the incidence of POST at 4 h as by this time the patents are generally awake, alert, and more cooperative to participate in the study. This is also in line with earlier studies.[6,13] Attenuation of POST at 2 h and not at 24 h post-operatively after pre-operative ketamine gargles was observed in women undergoing gynaecological surgeries. The authors measured serum ketamine levels intra-operatively and suggested that with such low levels of serum ketamine, the systemic absorption of ketamine was unlikely to have role in the attenuation of POST and rather suggested a topical effect of ketamine.[13] Ketamine gargle has been found to be effective in reducing the incidence and severity of POST due to its anti-inflammatory effects.[6] However, there are a few demerits of gargle ketamine over nebulization due to its bitter taste, large volume required for gargle with risk of aspiration if accidentally swallowed and patient cooperation. Honey is added to ketamine to mask the bitter taste

in children.[14] Our rationale 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.

The topical effect of ketamine nebulisation probably attenuated POST at 2 and 4 h post-operatively in the present study. The late onset of moderate pain in the control group reflects a more gradually developing local inflammation.

Other pharmacological agents used earlier, include aspirin gargles, benzydamine hydrochloride (BH) gargles, transdermal ketoprofen, lignocaine 10% spray, IV dexamethasone, beclomethasone gel on tracheal tube and magnesium lozenges. All have been shown to reduce the incidence and severity of POST up to 24 h post-operatively.[4,15-18] Betamethasone gel applied over the endotracheal tube (ETT) and ketamine gargle were found to be comparable in attenuating POST during the first 24 post-operative hours after elective surgical procedures. However, the incidence of post-operative cough and hoarseness of voice was attenuated better with betamethasone application.[17] Lignocaine spray decreased incidence of cough at tracheal extubation in surgeries of <2 h.[19] Medicated lozenges of licorice had efficacy of decreasing POST in smokers for surgery under GA of more than 1 h.[20] Recently, siccoral and strefen have been found to be effective in relieving POST in the early hours following extubation.[21] A meta-analysis found that the topical application of BH reduced the incidence of POST in patients following GA.[22] However, dipping of whole ETT cuff with benzydamine hydrochloride (BH) prior to anaesthesia induction had no influence on the incidence and severity of POST during 24 h post-operatively.[23] IV dexamethasone significantly reduced the risk and severity of POST at 24 h in a meta-analysis.[24] Use of budesonide inhalation suspension 200 mcg 10 min prior to intubation and 6 and 24 h after extubation in thyroid surgery under GA exhibited significantly less severe sore throat and hoarseness at 1 h and 24 h following extubation.[25] Gabapentin (100 mg) when administered orally, 1 h before anaesthesia had a lower incidence of POST than the placebo group (47% vs. 78%, $P = 0.038$).[26] Endotracheal intubation done with Glide Scope® video laryngoscope was found to attenuate POST in patients as compared to Macintosh blade with normal airway patients, at 6 and 24 h after surgery.[27]

During the use of wall-mounted oxygen driven nebulization the liquid is broken up into droplets by the compressed air. The aerosol produced is heterodisperse in size and is filtered within the nebulizer by baffles to remove the largest droplets.[28] The pneumatic nebulisation method produces larger particles (10–25 μm) which mostly deposit in the mouth and throat and for those of 5–10 μm diameter deposit in a transition from mouth to airway.[29] Deposition of aerosol in the mouth and upper airway probably reduced incidence and severity of POST due to topical analgesia, anti-inflammatory effect and NMDA receptor antagonist effect of nebulized ketamine.

We used well-defined inclusion and exclusion criteria and experienced anaesthesiologists performed tracheal intubation. The tracheal intubation was performed at TOF <2 and tracheal tube cuff inflation was maintained guided by peri-cuff leak at peak airway pressure of 20 cm H_2O.

There are a few limitations of our study. No formal sedation scale was used and we were also not able to measure plasma ketamine levels during the study period. We did not keep a record of the number of episodes of bucking at the time of extubation. Further, it would be interesting to compare the efficacy between ketamine nebulization and ketamine gargle. Bigger sample size in a similar could add strength to the findings.

CONCLUSION

The use of pre-operative ketamine nebulisation reduced the incidence and severity of POST during early post-operative period in patients receiving GA with tracheal intubation. This technique adds to the armamentarium of the anaesthetist in management of the 'little big problem' of POST.

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