

Original Research Article

Comparison of nebulized ketamine and ketamine with clonidine in postoperative sore throat

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ABSTRACT

Background: Postoperative sore throat (POST) consider a minor ailment in patients receiving general anesthesia with endotracheal intubation, seen in 21-65% cases but it causes significant distress and increases postoperative morbidity and patient dissatisfaction. This study was done to compare nebulized ketamine and ketamine with clonidine to treat POST.

Methods: This was a prospective, randomized, double-blind control clinical study. After approval from institution ethical and scientific committee, study was conducted in between May 2015-April 2016. Written and informed consent was obtained from 100 patients of either sex aged between 20-65 years. ASA I-II, undergoing surgery in supine position lasting up to two hour. Patients were randomized into two groups Group K (n=50) nebulized with 50 mg ketamine (1cc) + 3cc NS =4cc, Group KC (n=50) nebulized with ketamine 50mg (1cc) + clonidine 150µg (1cc) + 2cc NS for 15 min, before general anaesthesia with endotracheal intubation. The POST and hemodynamic variable were monitored before nebulization, after nebulization, before induction, on arrival to PACU and at 4, 8, 12, 24 hours post operatively. POST was graded on 4 point scale (0-3).

Results: Overall incidence of POST was 46% (Group K-40%, KC-6%). The Incidence and severity of POST were significantly attenuated in Group KC in comparison to Group K at 4 hours (P= 0.002), 8 hours (P=0.000), 12 hours (P= 0.000) and at 24 hours (P=0.000).

Conclusions: Preoperative nebulization with clonidine and ketamine mixture compared to ketamine is more effective in dealing with postoperative sore throat with no adverse effects.

Keywords: Clonidine nebulization, Endotracheal intubation, Ketamine, POST

INTRODUCTION

Postoperative sore throat is one of the most common complications after endotracheal intubation, which usually lingers for 12-24 hours after the operation.¹ The incidence is estimated to be of 18-65% in different studies.^{2,3} Factors contributing to development of POST include trauma to pharyngolaryngeal mucosa from

laryngoscopy, placement of nasogastric tube or oral suctioning.⁴ The cuff design and pressure may affect tracheal mucosal capillary perfusion.⁵ Contact of tracheal tube with vocal cords and posterior pharyngeal wall result in edema and mucosal lesion.⁶ Postoperative nausea and vomiting and harsh intubation.⁷ The common prophylactic measures used to decrease the incidence of POST include the use of smaller-sized endotracheal tubes

with a low intracuff pressure.⁸ Use of topical lidocaine,⁹ steroid coated tubes,¹⁰ gargling with azulene sulphonate ketamine and licorice.⁸⁻¹³ Ketamine is N-methyl d-aspartate (NMDA) receptor antagonist and has been used as gargle or nebulization.¹³⁻¹⁵ Various preclinical and clinical studies have reported that clonidine produces antinociception regardless of the route of administration (central or peripheral).¹⁶⁻¹⁹ Topical administration of clonidine elicits antinociception by blocking the emerging pain signals at peripheral terminals through alpha 2 adrenoceptors without producing the undesirable central side effect observed after systemic administration.²⁰ In a dose response study, it was demonstrated that iv clonidine 3µg/kg was more effective than clonidine 2µg/kg for postoperative pain relief after hemilaminectomy, while clonidine 5µg/kg resulted in same analgesia with significant side effects.²¹ Inhaled clonidine 75µg was used to treat broncho-obstructive diseases and found to improve basal respiratory functions without significantly influencing blood pressure.²²

Aim

To evaluate the difference between nebulized ketamine and nebulized ketamine with clonidine in postoperative sore throat.

Objectives

- Comparison of postoperative sore throat at 4 hours, 8 hours, 12 hours and 24 hours.
- Comparison of side effects between the two groups.

METHODS

This was prospective, double blind randomized clinical study. After approval from Institutional Ethical and Scientific Committee study was conducted in between May 2015-April 2016. Written informed consent was obtained from all the patients enrolled in the study. In the present study we compared effect of nebulized ketamine and ketamine with clonidine in post-operative sore throat in 100 patients.

Inclusion criteria

- Age group 20-65 years
- Either sex
- Physical status ASA I-II
- Surgery in supine position under GA lasting for up to two hours.

Exclusion criteria

- History of prior sore throat
- Patients using steroids or NSAIDS
- Patients with COPD, asthma
- Mallampati grade>2
- Patients with >2 attempts of intubation

- Pregnant women
- Patient and/or his/her legally acceptable representative not willing to provide their voluntary written informed consent for participation in the study

Patients were divided into two groups:

- Group K patients nebulized with ketamine 1cc (50mg) plus normal saline 3cc, so total volume was 4cc
- Group KC patients nebulized with ketamine 1cc (50mg) plus clonidine 1cc (150mg) plus normal saline 2cc, so total volume of 4cc. Randomization was done by anesthesiologist who was not the part of study further. In preparation room an i.v. cannula inserted to the patients. Nebulizing solution was prepared by one of the anesthesiologist not taken part in study further. Patients nebulized via compressor nebulizer for 15 minutes. Patients were blind to the nebulizing solution. Patients was then transferred to operation theatre, standard monitor was applied (non-invasive blood pressure, pulse oximetry, ECG besides capnography) after induction of anaesthesia. Patient was pre oxygenated with 5L/min O₂, 100% for 3-5 min, pre medication with glycopyrolate 0.01mg/kg, midazolam 0.02mg/kg. Induction was done with fentanyl 2µ/kg, propofol 2 mg/kg, endotracheal intubation was facilitated with succinylcholine 2mg/kg. Laryngoscopy attempted after 60-90 seconds, when fasciculation disappeared from patient's body. Endotracheal tube size was selected after laryngoscopy under direct visualization. All intubation was performed by an experienced anaesthesiologist. Endotracheal tube cuff was inflated until no exhalation sound or leak heard. Maintenance of anaesthesia done using isoflurane 1 MAC and atracurium in both the groups, O₂ 50%, and N₂O 50%. Extubation was performed using same method in both groups after surgery, inhalational anaesthetic turned off. Muscle relaxant reversed with neostigmine 0.05mg/kg, glycopyrolate 0.01mg/kg. Patient was extubated when fully conscious. In recovery room patient received O₂ 2.5L/min via face mask. The intensity of sore throat was recorded at 4, 8, 12 and 24 hours post operatively, first observation was recorded at 4 hours as patients became alert enough to take part in the study. Sore throat was measured on 4 points scale 0-3.12

0=no sore throat,

1=mild sore throat (complain of sore throat on asking)

2=moderate sore throat (complain of sore throat on his/her own)

3=severe sore throat (change in voice or hoarseness associated with throat pain)

Protocol for pain management- IV diclofenac 1.5 mg/kg every 8 hourly.

Statistical analysis

The data was initially captured in a customized proforma, then transferred to Microsoft excel spreadsheet. The online statistical software was used for analysis of the data. Proportional comparison between the two groups was done using Fisher's Exact test/Z-test for two sample proportion. Mean comparisons between the two groups was done using unpaired 't' test. A p-value of <0.05 was taken as statistically significant. The final data was presented in the form of tables and graphs.

RESULTS

100 patients of ASA I-II were studied in this prospective, randomized trial. Demographic data age, sex, weight, and ASA grading have depicted in Table 1 and Figure 1, have no significant difference between them. Patients in both the group remained hemodynamically stable with no complaint of nausea, vomiting, sedation, laryngospasm or any other side effect.

Table 1: Comparison of mean age and weight between ketamine-clonidine and ketamine alone groups (N=100).

Parameter	Group KC (Mean±SD)	Group K (Mean±SD)	't' value	p-value
Age	43.8±15.4	39.6±12.4	1.50, df=98	0.136, NS
Weight	67.2±10.2	67.16±9.30	0.00, df=98	1.000, NS

Unpaired 't' test applied. P-value <0.05 was taken as statistically significant, NS=Non-significant.

Table 2: Comparison of sore throat at different time intervals between Group KC and Group K (N=100).

Time Interval	N	Group KC		Group K		Z-value/Fisher exact test	P-value
		No.	%	No.	%		
4 hours	6	0.0	0.0	6	100.0	Fisher	0.002*
8 hours	15	2	13.3	13	86.7	-5.91	0.000*
12 hours	17	3	17.6	14	82.4	-4.95	0.000*
24 hours	8	1	12.5	7	87.5	-4.54	0.000*
Overall	46	6	13.1	40	86.9	-10.53	0.000*

Fisher Exact test/Z-test for two sample proportion applied. P-value<0.05 was taken as statistically significant.

Table 3: Distribution of Sore throat at different time intervals between Group KC and Group K according to severity (N=100).

Time interval	Severity	N	Group KC		Group K	
			No.	%	No.	%
4 hours	1	6	0	0.0	6	100.0
	2		0	0.0	0	0.0
8 hours	1	15	2	13.3	10	66.7
	2		0	0.0	3	20.0
12 hours	1	17	3	17.6	11	64.7
	2		0	0.0	3	17.6
24 hours	1	8	1	12.5	4	50.0
	2		0	0.0	3	37.5
Overall	1	46	6	13.1	31	67.4
	2		0	0.0	9	19.5

The mean age between the two groups was comparable (43.8±15.4 years in Group KC vs. 39.6±12.4 years in Group K) (P=0.136). The mean weight between the two groups was also comparable (67.2±10.2 kg in Group KC vs. 67.16±9.30 kg in Group K) (P=1.000) (Table 1). There were 64% females in Group KC and 60% in Group K, similarly there were 36% males in Group KC and 40% in Group K (Figure 1). At 4 hours, there was no incidence of sore throat in Group KC (0%), while it was

experienced by 6 patients in Group K. The difference was found statistically significant (P<0.05) (Table 2). At 8 hours, 15 patients experienced sore throat, 2 (13.3%) patients experienced sore throat in Group KC, and 13 (86.7%) patients of Group K. The difference was found to be statistically significant (P<0.05) (Table 2).

At 12 hours, 17 patients experienced sore throat, 3 (17.6%) patients experienced sore throat in Group KC,

while it was experienced by 13 (86.7%) of the patients of Group K. The difference was found to be statistically significant ($P<0.05$) (Table 2). At 24 hours, 8 patients experienced sore throat, 1 (12.5%) patients experienced sore throat in Group KC, while it was experienced by 7 (87.5%) of the patients of Group K. The difference was found to be statistically significant ($P<0.05$) (Table 2). Overall 46 patients experienced sore throat in the present study, of these higher proportion of the patients of Group KC 40 (86.9%) experienced sore throat in comparison to the Group K 6 (13.1%). The difference was found to be statistically significant ($P<0.05$) (Table 2).

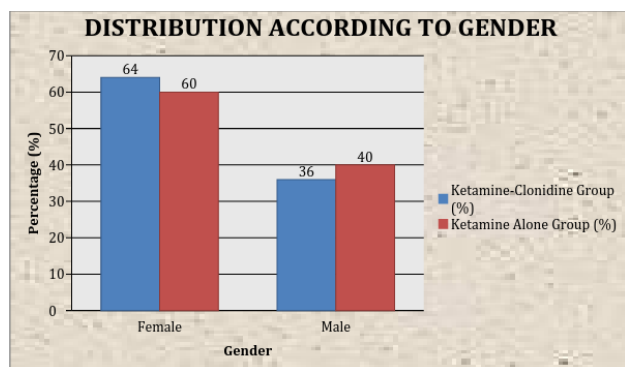


Figure 1: Bar diagram showing distribution according to gender in both the groups.

There was an overall incidence of sore throat in 46 patients. Of these 46, 6 patients of Group KC reported sore throat, and all these patients had a severity score of 1. While 40 patients reported sore throat in the Group K, 31 (67.4%) had severity of 1 and 9 (19.5%) reported severity of score 2 (Table 3).

DISCUSSION

The present study was designed to evaluate difference in the effect of nebulised ketamine and ketamine with clonidine in postoperative sore throat- effect was observed on the incidence and severity of POST at 4, 8, 12, 24 hours following general anesthesia, with tracheal intubation lasting up to 2 hours. In present study total incidence of POST was 46% compared 18-65% in previous studies.² Out of which it was 6% in Group KC and (40%) in Group K, significantly less in Group KC ($P=0.000$).

The incidence and severity of POST was significantly less in Group KC than in Group K at the following time intervals, 4 hours after extubation ($P=0.002$), 8 hours after extubation ($P=0.000$), 12 hours after extubation ($P=0.000$) and 24 hours after extubation ($p=0.05$). In a study, nebulised ketamine was found to be better than saline to attenuate the POST, at 2 hours.¹⁵ 6 patients in saline and 0 patients in ketamine group ($P=0.02$) and at 4 hours, 13 patients in saline and 4 patients in ketamine group ($P=0.03$) had POST. In present study 6 patients in ketamine group had POST, comparable outcome but 0

patient in group KC has POST. Decreased incidence and severity of POST suggestive that co administration of ketamine and clonidine for nebulisation was effective at early hours and also for prolonged period. Among the various reasons of POST airway inflammation following airway mucosal injury, airway smooth muscle contraction contributed to the problem significantly.^{4,6,8} The analgesia due to ketamine was achieved through topical action of ketamine via NMDA antagonistic action and anti-inflammatory action.^{14,23-26} Experimental animal studies have shown that ketamine has protective effect on airway inflammatory injury and also relaxes airway smooth muscles probably via interference with Ca^{+} .¹⁴ Addition of clonidine to ketamine in nebulizing solution gave better results was not only due to synergistic topical action of ketamine and clonidine but long terminal half-life of clonidine also contributed to such result.^{23,27}

Combination of oral clonidine and low dose intravenous ketamine reduces the consumption of morphine through patient controlled analgesia after spine surgery suggesting that interaction of ketamine and clonidine does exist, because these drugs acts via different mechanism.²⁸ Dogrul and colleagues demonstrated that topical clonidine elicit anti-nociception by blocking the emerging pain signals at peripheral terminals through α_2 adrenoceptors without producing undesirable central side effect Inhaled clonidine found to be bronchoprotective in a study done in asthmatic patients by Lindgren et al.^{20,22} As both the drugs were used through nebulisation concentration achieved around airway would be high and produced effective outcome, possibly due to synergistic action of ketamine clonidine Group KC had better analgesia than Group K. There are a few limitations of present 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 with clonidine nebulization. Bigger sample size in a similar could add strength to the findings.

CONCLUSION

Preoperative nebulization with clonidine and ketamine mixture compared to ketamine is more effective in dealing with postoperative sore throat with no adverse effects. This technique adds to the armamentarium of the anaesthetist in management of the 'little big problem' of POST. Further studies, regarding time and dose-ranging studies with larger study populations, are needed to compare ketamine nebulization and ketamine with clonidine nebulization to prevent the POST after general anesthesia in an ambulatory care setting.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

- Jensen PJ, Hommelgaard P, Søndergaard P, Eriksen S. Sore throat after operation: influence of tracheal intubation, intracuff pressure and type of cuff. *Br J Anaesth.* 1982;54(4):453-7.
- Chandler M. Tracheal intubation and sore throat: a mechanical explanation. *Anaesthesia.* 2002;57(2):155-61.
- Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg.* 1999;89(3):652-8.
- Monroe MC, Gravenstein N, Saga-Rumley S. Postoperative sore throat: effect of oropharyngeal airway in orotracheally intubated patients. *Anesth Analg.* 1990;70(5):512-6.
- Kim TK, Min JJ, Seo JH, Lee YH, Ju JW, Bahk JH, et al. Increased tracheal cuff pressure during insertion of a transoesophageal echocardiography probe: A prospective, observational study. *Eur J Anaesthesiol.* 2015;32(8):549-54.
- Al-Qahtani AS, Messahel FM. Quality improvement in anaesthetic practice- incidence of sore throat after using small tracheal tube. *Middle East J Anaesthesiol.* 2005;18(1):179-83.
- McHardy FE, Chung F. Postoperative sore throat: cause, prevention and treatment. *Anaesthesia.* 1999;54(5):444-53.
- Stenqvist O, Nilsson K. Postoperative sore throat related to tracheal tube cuff design. *Can Anaesth Soc J.* 1982;29(4):384-6.
- Kalil DM, Silvestro LS, Austin PN. Novel preoperative pharmacologic methods of preventing postoperative sore throat due to tracheal intubation. *AANA J.* 2014;82(3):188-97.
- Ayoub CM, Ghobashy A, Koch ME, McGrimley L, Pascale V, Qadir S, et al. Widespread application of topical steroids to decrease sore throat, hoarseness, and cough after tracheal intubation. *Anesth Analg.* 1998;87(3):714-6.
- Sumathi PA, Shenoy T, Ambareesha M, Krishna HM. Controlled comparison between betamethasone gel and lidocaine jelly applied over tracheal tube to reduce postoperative sore throat, cough, and hoarseness of voice. *Br J Anaesth.* 2008;100(2):215-8.
- Ogata J, Minami K, Horishita T, Shiraishi M, Okamoto T, Terada T, et al. Gargling with sodium azulene sulfonate reduces the postoperative sore throat after intubation of the trachea. *Anesth Analg.* 2005;101(1):290-3.
- Canbay O, Celebi N, Sahin A, Celiker V, Ozgen S, Aypar U. Ketamine gargle for attenuating postoperative sore throat. *Br J Anaesth.* 2008;100(4):490-3.
- 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.
- Ahuja V, Mitra S, Sarna R. Nebulized Ketamine decrease incidence and severity of post-operative sore throat. *Indian J Anaesth.* 2015;59(1):37-42.
- Buerkle H, Schäpsmeier M, Bantel C, Marcus MA, Wüsten R, Van Aken H. Thermal and mechanical antinociceptive action of spinal vs peripherally administered clonidine in the rat inflamed knee joint model. *Br J Anaesth.* 1999;83(3):436-41.
- Gentili M, Juhel A, Bonnet F. Peripheral analgesic effect of intra-articular clonidine. *Pain.* 1996;64(3):593-6.
- Gentili M, Houssel P, Osman D, Henel A, Juhel A, Bonnet F. Intra-articular morphine and clonidine produce comparable analgesia but the combination is not more effective. *Br J Anaesth.* 1997;79:660-1.
- Giannoni C, White S, Enneking FK, Morey T. Ropivacaine with or without clonidine improves pediatric tonsillectomy pain. *Arch Otolaryngol Head Neck Surg.* 2001;127(10):1265-70.
- Dogrul A, Uzbay IT. Topical clonidine antinociception. *Pain.* 2004;111(3):385-91.
- Hirota K, Lambert DG. Ketamine: new uses for an old drug? *Br J Anaesth.* 2011;107(2):123-6.
- Zhu MM, Qian YN, Zhu W, Xu YM, Rong HB, Ding ZN, et al. Protective effects of ketamine on allergen-induced airway inflammatory injure and high airway reactivity in asthma: experiment with rats. *Zhonghua Yi Xue Za Zhi.* 2007;87(19):1308-13.
- Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schüttler J. Differential modulation of remifentanyl-induced analgesia and post-infusion hyperalgesia by S-ketamine and clonidine in humans. *Anesthesiology.* 2003;99(1):152-9.
- Nitta R, Goyagi T, Nishikawa T. Combination of oral clonidine and intravenous low-dose ketamine reduces the consumption of postoperative patient-controlled analgesia morphine after spine surgery. *Acta Anaesthesiol Taiwan.* 2013;51(1):14-7.

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