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Evaluation of Safety and Efficacy of Ketamine Nebulization to Reduce Post-operative Sore Throat in Patients Undergoing General Anesthesia-Prospective Randomized Single Blind Placebo Controlled Study

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ABSTRACT

Postoperative sore throat (POST) affects between 21 to 65% of individuals. Ketamine, which was formerly used as a gargle to reduce POST, has limits. The purpose of this study was to determine whether nebulized ketamine lowers POST. A prospective, randomized, placebo-controlled, double-blind study was carried out. 60 individuals with signed informed permission who were between the ages of 20 and 60 and of either sex and had physical status I-II according to the American Society of Anesthesiologists were included. Patients were divided into two groups by randomization; group N got 5.0 mL of saline nebulization and group K received 1.0 mL of ketamine 50 mg along with 4.0 mL of saline nebulization for 15 min. Ten minutes after the patients' nebulization was finished, GA was induced. Prior to nebulization, before induction, at arrival in the post-anesthesia care unit and at 2, 4, 6, 8 and 24 hrs after surgery, POST and hemodynamic monitoring were performed. On a scale from 0 to 3, POST received a grade. Incidence and severity of POST were significantly less in Group K as compared to Group N (p value<0.05) at 4, 6, 12 and 24th post operative hours. Hemodynamic parameters were comparable in both the groups. Ketamine nebulization significantly attenuated the incidence and severity of POST, especially in the early post operative period, with no adverse effects.

INTRODUCTION

Although clinicians generally perceive post-operative sore throat (POST) as a minor consequence, it is a regular occurrence following general anesthesia[1]. Postoperative sore throat has the potential to reduce not just patient satisfaction but also the necessity for additional pain medication in the post anesthesia care unit[2]. Although the symptoms disappear on their own without therapy, preventive intervention to reduce their frequency and severity is still advised[3].

Airway instruments (tracheal intubation) are the most common source of trauma to the pharyngeal and tracheal mucosa, resulting in irritation and inflammation of the airway and postoperative sore throat[4]. Other variables that may contribute to POST include a lack of airway humidity, suctioning, high anesthetic air flow rates and surgical manipulation of the airway and associated tissue[5]. Many factors involved in POST, including as type of airway device, manner of insertion, use/type of lubricant, airway design, cuff pressure, length of operation, anesthesia provided and a variety of patient attributes, contribute to the significant diversity of incidence (21-60%). The occurrence is the highest with tracheal tube insertion (45.4%) followed by patients with laryngeal mask airway insertion (17.5%), while patients with facemask have the lowest occurrence of sore throat (3.3%).

Recently, quality assurance of anesthesia has become increasingly important for improving postoperative sore throat so various pharmacological and non-pharmacological trials have been used for attenuating postoperative sore throat with variable success. Pharmacological measures include use of beclomethasone inhalation, gargling with azulene sulfonate, local spray with lidocaine and intracuff administration of alkalized lignocaine, topical methylprednisolone, diclofenac polyamine patch, transdermal ketoprofen and application of triamcinolone acetonide paste[6]. These all techniques have their own limitations and success rate. Non pharmacological measures include use of smaller sized endotracheal tubes, lubricating the endotracheal tube with water soluble jelly, careful airway instrumentations, intubation after full relaxation, gentle oropharyngeal suctioning, minimizing intra cuff pressure and extubating when the tracheal tube cuff is fully deflated[7].

N-methyl-D-aspartate (NMDA) is known to play a function in nociception and inflammation. NMDA receptors can be present in both the central nervous system and the peripheral neurons. Ketamine is an NMDA receptor antagonist that has been linked to antinociception and an anti-inflammatory cascade[6].

Ketamine has been utilized to reduce the occurrence and severity of POST by nebulization as well as gargle. Nebulized ketamine saves the patient from the harsh taste of ketamine and requires a far less amount than gargle, which risks aspiration if unintentionally eaten[8].

Present study is aimed at reduction of incidence and severity of POST after ketamine nebulization in patients undergoing general anesthesia with endotracheal intubation.

MATERIALS AND METHODS

This prospective observational study was carried out by Anesthesiology department, at Sir Takhtsinhji hospital, Government Medical College, Bhavnagar, Gujarat, India. This present study was conducted in accordance of International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, catering for all its precautions. This study was approved by the Institution Review Board / Institutional Ethics Committee with number 1000/2020. Study was conducted January 2021 to June 2021 after taking written and informed consent from all the patients.

All patients undergoing general anesthesia were enrolled based on following inclusion and exclusion criteria. Inclusion criteria were Aging between 20-60 years, with American society of Anesthesiology (ASA) classification Grade I-III, either gender and patients undergoing general anesthesia in supine position lasting >90 min. Exclusion criteria were patients refusing to give consents, patients with a history of pre-operative sore throat, oral surgeries, asthma, chronic obstructive pulmonary disease, >ASA grade >3, known allergies to study drug, patient on treatment with non-steroidal anti-inflammatory drugs, those who required more than one attempt at intubation.

After taking written informed consent in the local language, patients who were posted for General anesthesia with endotracheal intubation, randomized using computer generated random number sequence methods in two groups.

- **Group K:** Nebulization was done with Ketamine 50 mg (1 mL) plus normal saline 4 mL
- **Group N:** Nebulization was done with normal saline (5 mL)

After shifting the patient to the pre anesthetic care room, 20 G intravenous catheter is inserted on non-dominant hand. Baseline parameters like ECG for heart rate (HR), non-invasive blood pressure (NIBP), mean arterial pressure (MAP) and pulse oximetry for oxygen saturation (SPO_2) were recorded before and after giving nebulisation at 5 min, 10 min and 15 min. Patients were shifted to operation theatre after 15 min of giving nebulisation. Patients were premedicated with inj. ondansetron 0.08 mg kg^{-1}, inj. glycopyrrolate

4 mcg kg^{-1}, inj. Midazolam 0.02 mg kg^{-1} and inj. Fentanyl 1 mcg kg^{-1} and preoxygenated with 100% oxygen for 3 min. Patients were induced with inj. Propofol 2-2.5 mg kg^{-1} IV slowly and inj. Succinyl choline 2 mg kg^{-1} till loss of eyelash reflex, jaw relaxation, absence of movements and apnoea. Patients were ventilated with Bain's circuit. A brisk and gentle laryngoscopy were done by using a Macintosh laryngoscope blade (size 3 or 4). Trachea were intubated with a sterile, single lumen cuffed polyvinyl chloride endotracheal tube. Cuff was inflated with a volume of air until no air leakage was audible or palpable. General anaesthesia was maintained with oxygen, nitrous oxide, sevoflurane, intermittent positive pressure ventilation and inj. Vecuronium.

At the end of surgery, analgesia was supplemented with inj. Paracetamol 10 mg kg^{-1} and oropharynx was suctioned with care, using a soft, disposable suction catheter. Neuromuscular blockage was reversed with inj. Neostigmine 50 mcg kg^{-1} and inj. Glycopyrrolate 10 mcg kg^{-1} iv. The endotracheal cuff was deflated properly and tube was removed after the patient regained complete consciousness.

After shifting the patient to the post anaesthesia care unit (PACU), post operative sore throat was assessed by another anaesthetist at 0, 2, 4, 6, 12 and 24 hrs postoperatively for the incidence and severity.

Post operative sore throat was graded on a four-point scale.

- **Grade 0:** No sore throat
- **Grade 1:** Complain of mild sore throat only on asking
- **Grade 2:** Complain of sore throat on his/her own
- **Grade 3:** Severe sore throat (change in voice associated with throat pain)

Even after 24 hrs if patients still had moderate to severe sore throat, saline gargle and decongestants were prescribed.

RESULT

The p-value is >0.05 i.e., 0.44 and is not statistically significant. So, mean age in both the groups was comparable. P value for gender distribution in both the groups is 0.79 (p value>0.05) and is not statistically significant (Table 1).

Incidence of post operative sore throat at 0 and 2nd postoperative hours were comparable in both the groups (p value>0.05). Incidence of post operative sore throat at 4th, 6th, 12th and 24th hrs were significantly less in group K compared to group N (p value<0.05). (Table 2)

The unpaired t-test showed no statistical difference in the study groups. Both groups were comparable.

Table 1: Demographic data

Parameter	Group K (n = 30)	Group N (n = 30)	p-value
Age (Year)	40.4±10.58	38.5±7.73	0.44
Gender			
Male	15	17	0.79
Female	15	13	

Table 2: Incidence of post operative sore-throat in study groups

Time	Sore throat	Group K	Group N	p-value
0 hrs	Absent	18	15	0.60
	Present	12	15	
2hrs	Absent	23	16	0.10
	Present	07	14	
4 hrs	Absent	26	18	0.03
	Present	04	12	
6 hrs	Absent	26	18	0.03
	Present	04	12	
12 hrs	Absent	28	19	0.01
	Present	02	11	
24 hrs	Absent	29	21	0.01
	Present	01	09	

Table 3. Severity of post operative sore-throat in two study groups

Post op hour	Group	Grade 0	Grade 1	Grade 2	Grade 3	p-value
0 hrs	K	18	10	2	0	0.72
	N	15	12	3	0	
2 hrs	K	23	6	1	0	0.16
	N	23	12	2	0	
4 hrs	K	26	3	1	0	0.04
	N	18	11	1	0	
6 hrs	K	26	4	0	0	0.03
	N	18	12	0	0	
12 hrs	K	28	2	0	0	0.01
	N	19	11	0	0	
24 hrs	K	29	1	0	0	0.01
	N	21	9	0	0	

Table 4: Hemodynamic analysis: comparison of pulse rate in study groups

Time	Group K	Group N	p-value
BEFORE NEB	81.4±9.47	82.6±10.58	0.64
AT5 MIN.	82.86±8.92	84.93±8.90	0.37
AT10 MIN.	83.06±8.72	85.4±6.56	0.24
AT15 MIN.	85.38±7.58	87.13±4.86	0.28

At immediate post-operative hour, severity of post operative sore throat was comparable in both the groups (p value>0.05). At 2nd post-operative hour, severity of post operative sore throat was comparable in both the groups (p value>0.05). At 4th post-operative hour, severity of post operative sore throat was not comparable in both the groups (p value<0.05). At 6th post-operative hour, severity of post operative sore throat was not comparable in both the groups (p value<0.05). At 12th and 24th post-operative hours, severity of post operative sore throat was statistically significantly low in group K as compare to Group N (p value<0.05) (Table 4).

DISCUSSION

Post-operative sore throat (POST) is a common complaint following endotracheal intubation, resulting in substantial patient pain and dissatisfaction with the quality of care[9]. It might be caused by mucosal damage in the trachea as well as other variables such as oropharyngeal suctioning, intracuff pressure, use of a throat pack and endotracheal tube size[10,11]. POST risk factors include surgical duration, difficulty in intubation, use of a stylet and prone posture[12]. Many

research have been performed to mitigate this problem, with varying degrees of success, employing various approaches to reduce POST[6,8,13].

A research conducted in 2005 suggested Nonpharmacological methods include lubricating the endotracheal tube with water-soluble jelly, careful airway instrumentation, intubation after full relaxation, gentle oropharyngeal suctioning, minimizing intracuff pressure and extubating when the tracheal tube cuff is fully deflated[14].

Several studies have been conducted using pharmacological methods to reduce POST, such as the widespread application of betamethasone gel over the tracheal tube (18) and the prophylactic use of dexamethasone 0.2 mg kg^{-1} intravenously, which significantly reduces the incidence and severity of sore throat[15].

Ketamine has been demonstrated to be a potential medication for POST reduction. It is a phencyclidine analogue. It is an N-methyl-D-aspartic acid (NMDA) receptor noncompetitive antagonist. The central nervous system (CNS) and sections of the limbic system are the principal sites of action. NMDA receptors are known to have a function in inflammation and nociception. NMDA receptors can be present in both the CNS and the peripheral nerves. POST is prevented by peripherally given NMDA receptor antagonists, which are implicated in the antinociception and anti-inflammatory cascade[16].

Ketamine has been used as a gargle and in nebulized form to reduce the frequency and intensity of POST. Nebulization is claimed to be superior than gargle because it is a simpler method of administering the treatment, a lower volume of drug is required and patient participation is improved. There is also no danger of aspiration with nebulization[18]. Ketamine is known to stimulate the sympathetic nervous system, although topical use has a lower possibility of systemic absorption and consequently less negative effects.

In the present study, Incidence of POST (Table 3) were comparable in both the groups at 0 and 2nd post operative hours (p-value>0.05), while incidence of POST was significantly less in Group K as compared to Group N at 4, 6, 12 and 24th hrs postoperatively (p value<0.05). This result was in consonance with a previously done study by Khilji *et al*.[10] in which they used preoperative ketamine (50 mg) nebulization to reduce POST and they found significantly less incidence of POST at 2, 4, 6, 12 and 24th hour post operatively. This significant decrease in the incidence of POST may be due to the anti-inflammatory and antinociception effects of ketamine through N-methyl-D-aspartic acid (NMDA) receptors[17]. The difference in the result at 2nd post operative hour may be due to less sample size we had (No. of study participants 60) as compared to the study done by Khilji *et al*.[10] (No. of participants 96).

Table 5: Hemodynamic analysis: comparison of mean arterial pressure in study groups

Time	Group K	Group N	p-value
Before NEB	74.29±6.23	73.8±4.23	0.71
At 5 min	73.4±4.14	72.8±3.73	0.55
At 10 Min	72.2±4.40	70.2±3.72	0.06
At 15 Min	68.8±4.38	69.73±4.47	0.41

In the present study, severity of POST (Table 4) was comparable in both the groups at 0 and 2nd post operative hours (p value>0.05), while severity of POST was significantly less in Group K as compared to Group N at 4, 6, 12 and 24th hrs postoperatively (p value<0.05). This may be due to the topical analgesic, anti-inflammatory and NMDA receptor antagonistic effect of ketamine[9]. This result was in consonance with a previously done study by Charan *et al*., in which they used preoperative ketamine nebulization in different doses to decrease the severity of post operative sore throat in surgeries under General Anesthesia patients and concluded that severity of POST was significantly reduced in Group K1, K2 (ketamine) as compared to Group S (saline) at 2, 4, 8, 12 and 24th hr post operatively. The difference in the result at 2nd post operative hour may be due less sample size we had (No. of participants 60) as compared to the study done by Caran *et al*. (No. of participants 150).

In the Present study, Hemodynamic parameters like pulse rate (Table 5) and mean arterial pressure were comparable in both the groups (p value>0.05). These findings were in consonance with a study done by Mitra *et al*.[9] in which they used pre operative ketamine nebulization to reduce POST. This may be due to nebulized ketamine has less chances of side effects due to less systemic absorption.

The limitations of present study are that we did not follow up the patients for post-operative sore throat for a period more than 24 hrs, endotracheal tube cuff pressure monitoring was note done and also the serum concentration of the drugs could not be measured. We recommend such more studies to determine the safety and efficacy of ketamine nebulization to reduce post operative sore throat.

CONCLUSION

From the present study, it is concluded that Preoperative administration of nebulized ketamine effectively attenuates the incidence and severity of post operative sore throat in patients undergoing general anesthesia with endotracheal intubation with no significant hemodynamic changes.

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