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Evaluation of prophylactic ketamine gargle for the attenuation of postoperative sore throat following general anaesthesia with orotracheal intubation: A prospective randomized control study

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Abstract
Background: Post-operative sore throat is well known complication of endotracheal intubation. Ketamine gargle is a newly proposed adjunct for reducing the incidence of POST in anesthesia so we planned a study to find out the effectiveness of ketamine gargle with normal saline for prevention of postoperative sore throat (POST) after orotracheal intubation and compared with normal saline.
Material and Methods: Sixty patients aged between 18-60 years with American Society of Anaesthesiologists I and II, undergoing elective surgical procedures performed under general anaesthesia were randomly divided into two groups of 30 patients in each. Group S received 30 ml of normal saline and Group K received 40 mg of Ketamine in 30 ml of normal saline. All the patients were asked to gargle with the preparation for 30 sec after their arrival in the operation room 5 min before induction of anaesthesia. On arrival in the post-anaesthetic care unit (0 hr), at 2 hr, at 4 hr and at 24 hr thereafter, the patients were questioned by a blinded investigator whether he/she had experienced sore throat or any side-effect.
Results: In Group S POST occurred more frequently as compared to Group K, at 0hr, 2hr, 4hr and 24 hr and significantly more patients suffered severe POST in Group S at 4hr and 24 hr compared with Group K ($P<0.05$).
Conclusion: Ketamine gargle significantly attenuated POST, with no drug-related side effects.

Keywords: intubation; ketamine; postoperative sore throat

Introduction

Endotracheal intubation is the most important step of general anaesthesia. Postoperative sore throat (POST) and hoarseness of voice are minor but frequent complication of endotracheal intubation with reported incidence 10-85% [1, 2, 3]. POST is undesirable complication after general anesthesia which sometime required treatment. It is may be due to lack of airway humidity, trauma during intubation, suctioning, different sizes of endotracheal tubes, cuff pressure, high anaesthetic air flow rates and surgical manipulation of airway.

Various pharmacological and non-pharmacological measures have been used to attenuate the sore throat after general anaesthesia with varied success rate. Use of small sized endotracheal tube, careful orotracheal intubation, spraying the endotracheal tube cuff with lidocaine, intubation after full relaxation, gentle oropharyngeal suction, minimizing intra cuff pressure and gargling with aspirin and azulene sulfonate have been reported to decrease incidence of post- operative sore throat [3, 4, 5, 8] but the quest for a better simple, safe and inexpensive agent is always on.

Ketamine gargle is a newly proposed adjunct for reducing the incidence of POST in anesthesia. Gargling is a simple and easy method with less time requirement and can be performed by most of the patients. The aim of this study was to evaluate the efficacy of prophylactic ketamine gargles regarding attenuation of POST in patients undergoing the orotracheal tube intubation.

Method

After institutional ethical committee approval and Clinical Trials Registry-India (CTRI/2018/05/013895) registration, this randomized, double blinded, comparative study was conducted in department of anaesthesia, RNT medical college Udaipur (Raj.). Sixty patients aged 18-60 years of ASA grade I and II, belonging to either sex, scheduled for elective surgery under general orotracheal anaesthesia were enrolled for the study. Patients with a history of pre-operative sore throat, asthma, drug allergy, recent NSAIDs use, recent upper and lower respiratory tract infection, patients requiring more than one attempt or more than 15 sec for intubation and with mallampatti grade III and IV were excluded from study.

On the basis of previous study by Rudra A *et al.* [3] in which at 80% study power and alpha error of 0.05, detecting a difference of 35% in incidence of post-operative sore throat in two groups, ketamine gargle group and normal saline group, required 21 patients in each group as sample size. To compensate for the drop outs 30 patients were included in each group.

The study population was randomly allocated into two groups of 30 patients each using computer-generated table of random numbers which were kept in opaque sealed envelopes prepared by an anesthesiologist who did not participate in further study. Group-S (control group) -

patients were asked to gargle for 30 second with 30 ml of normal saline and Group-K (Ketamine group) - Patients were asked to gargle for 30 second with 40 mg preservative free ketamine in 30 ml of normal saline.

After explaining the procedure in detail and taking written informed consent, all patients were asked to gargle for 30 second according to group allocation 5 min before induction of anaesthesia. Standard monitoring was applied including Electrocardiogram (ECG), Noninvasive blood pressure (NIBP), Pulse oximetry (SpO_2). Patients were premedicated with inj midazolam 0.1mg/kg i.v, inj glycopyrrolate 0.01 mg/kg i.v. and preoxygenated with 100% oxygen for 3 minutes. Anaesthesia was induced with inj. propofol 2 mg/kg i.v. followed by inj. vecuronium 0.1 mg/kg i.v. for muscle relaxation. Patients were ventilated with 100% oxygen by bag and mask for 5 min and intubated with a soft seal cuffed sterile polyvinyl chloride endotracheal tube with a standard cuff and an internal diameter 7 – 7.5 mm ID for female and 8 - 8.5 mm ID for male under direct laryngoscopy vision. The endotracheal tube was inflated until no air leakage could be heard. Anaesthesia was maintained with oxygen 33%, nitrous oxide 67%, and isoflurane (0.8-1%). inj. vecuronium 0.05 mg/kg i.v. (repeated as required). After completion of surgery, inj glycopyrrolate 0.01mg/kg and inj neostigmine 0.05mg /kg was administered i.v. to reverse the neuro-muscular block. Intraoperatively, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and oxygen saturation (SpO2) measured before induction and after induction at 0, 5,15,30,45 60 90 min and at end of surgery. Oropharyngeal suction was carried out under direct vision to avoid injury to tissues before extubation. In post anaesthetic care unit (PACU) the patients were questioned by a blinded investigator at 0 hr, 2ndhr, 4thhr and 24thhr, whether they experienced sore throat or any other side effect.

POST was graded on four-point scale (0-3) [1, 2, 3] -

0. No sore throat.
1. Mild sore throat (complaints of sore throat only on asking)
2. Moderate sore throat (complaints of sore throat on his/her own)
3. Severe sore throat (Change of voice or hoarseness, associated with throat pain)

Statistical Analysis

Data were entered into MS-EXCEL and analyzed using SPSS version 20. Qualitative / Categorical like gender; ASA grade variables were summarized as frequency and percentage and were analyzed using chi square test or Fischer exact test as applicable.

Quantitative variables like weight, BP and HR were summarized as mean and standard deviation and were analyzed using unpaired student t test. A p value <0.05 was taken as statistically significant.

The primary outcome measured was the incidence of postoperative sore throat (POST). The secondary outcomes measured were severity of POST and effects on haemodynamic variables.

Results

Both the groups were comparable in terms of distribution of age, gender, ASA grading, body weight, smoking habits, duration of endotracheal intubation and duration of surgery (Table-1). Both groups were also comparable regarding intraoperative haemodynamic variables as SBP, DBP, HR and SpO2 (Figure-1, 2, 3).

Incidence of postoperative sore throat was significantly lower in group K compared to group S at all observed time periods (Table-2). Severity of sore throat as judged by patients was much lesser in ketamine group K as compared to saline group S (Figure-4).

Table 1: Characteristics of the study population

Characteristics	Group K (n=30)	Group S (n=30)	P value
Sex			
Male	11	13	
Female	19	17	0.598
Age (yrs) Mean±SD	54.1±13.5	36.7 ± 12.5	0.317
Weight (Kg) (mean ± SD)	63.2 ± 9.2	63.8 ± 8	0.811
Hight (cm) (mean ± SD)	162.9 ± 8.3	163.7 ± 8.2	0.719
ASA Grade			
I	24	23	
II	6	7	0.754
Smoking habits			
Yes	28	28	1
No	2	2	
Duration of surgery (min)	71.4 ± 27	68.8 ± 25.9	0.709
Duration of endotracheal intubation	75.8 ± 27.1	72.8 ± 25.9	0.666

Table 2: Comparison of incidence of POST at different time among study group

Time	Group K		Group S		P value
	No.	%	No.	%	
0 hour	14	46.7	23	76.7	0.034*
2 hour	12	40	21	70	0.038*
4 hour	8	26.7	19	63.3	0.009*
24 hour	6	20	16	53.3	0.016*

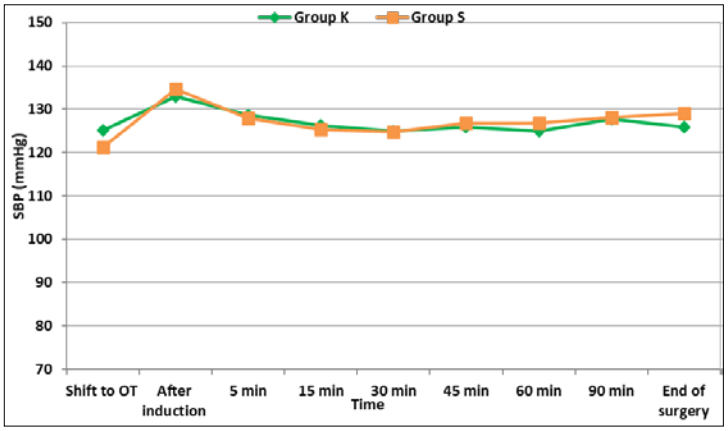

Fig 1: Comparison of intraoperative systolic blood pressure

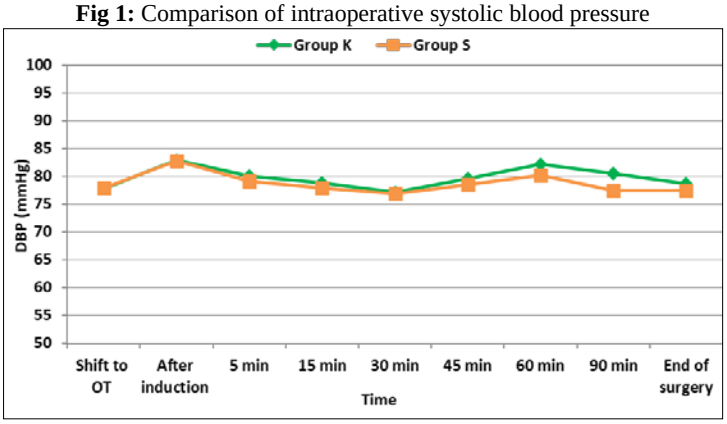

Fig 2: Comparison of intraoperative diastolic blood pressure

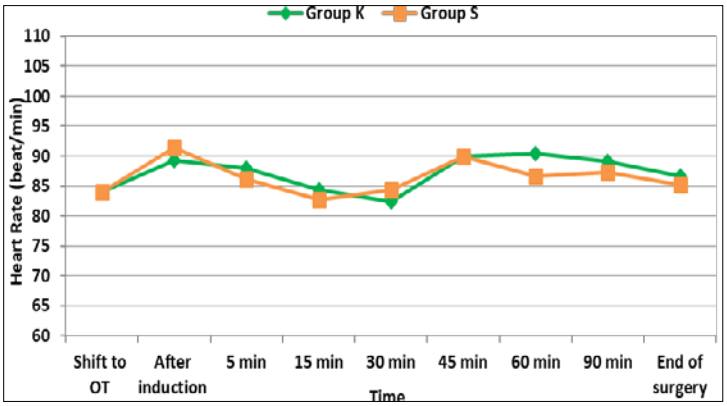

Fig 3: Comparison of intraoperative heart rate

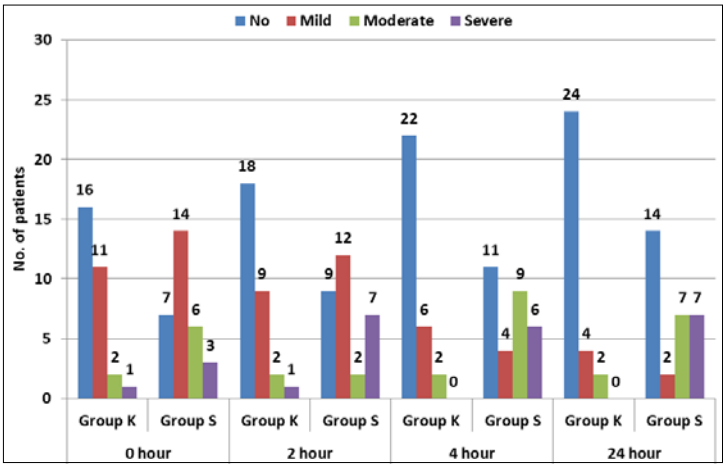

Fig 4: Post-operative sore throat among study groups

Discussion

Postoperative sore throat (POST) is a well-recognized but minor complication of tracheal general anaesthesia [9]. Prophylactic management for decreasing its frequency and severity is still recommended to improve the quality of post anaesthesia care though the symptoms resolve spontaneously without any treatment [7].

POST is a parsimonious description representing a broad constellation of signs and symptoms of laryngitis, tracheitis, hoarseness, cough and dysphagia [2] with incidence varying from 10%-85% after endotracheal intubation [1]. POST is resolved spontaneously without specific treatment in most of cases but sometime requires treatment. POST can be attenuated by non-pharmacological and pharmacological interventions. Identification of the factors associated with an increased risk of POST allows anaesthesia providers to avoid controllable factors, decrease the incidence of POST and improve patient anaesthetic outcomes. Many pharmacological interventions like steroids, non-steroidal anti-inflammatory drugs (NSAIDS), lignocaine etc. have been used to attenuate POST by various authors but had their own limitations.

Ketamine is noncompetitive NMDA antagonist which has been found by various authors to attenuate POST [2, 3, 10, 11, 12]. An increasing amount of experimental data shows that NMDA receptors are found not only in the central nervous system but also in the peripheral nerves. Peripherally administered NMDA receptor antagonists are involved with anti-nociception and anti-inflammatory cascade [2, 13, 14] by reducing NFκappa β activity, TNF-α (tumour necrosis factor

α) production [15], expression of inducible nitric oxide synthase [16] serum C-reactive protein, IL-6 and IL-10 [17]. Pharmacological studies reveal that low dose ketamine especially in the 'sub-psychotomimetic' range (blood concentration < 50 nanogram/ml) has 'anti-hyperalgesic', 'anti-allodynic' and possibly opioid 'tolerance-protective' effect due to an additive effect with opioids which is attributed to presynaptic opioid inhibition reducing afferent transmission by diminished transmitter release, and postsynaptic NMDA blockade which reduces wind up and central sensitization [18].

In our study, the overall incidence of POST in ketamine group (Group K) varied from 20 to 46.7% and from 53.7 to 76.7% in control group (group S) at different time interval which is in line with Canbay *et al*. [2] Rudra A *et al*. [3] and Shrestha SK *et al*. [11] studies. Moreover, the severity of POST was also reduced after preoperative gargling with ketamine compared to saline gargling.

Various factors implicated in causation of sore throat includes patient age, sex, use succinylcholine, large tracheal tube, cuff design and intracuff pressure [19, 20].

The cause of sore throat may be due to localized trauma leading to aseptic inflammation of pharyngeal mucosa. It may be associated with edema, congestion and pain [21].

In our study tracheal suctioning was done under direct vision with help of laryngoscope and utmost care was taken to minimize any trauma to pharyngeal mucosa.

Reduction of inflammation by ketamine gargles may be the reason for decrease in POST in our study. The ketamine gargle is hypothesized to provide analgesia due to its inhibition of N-methyl-d-aspartate (NMDA) receptors and agonist activity at opioid receptors located in the oral and the upper respiratory tract mucosa [22, 23].

In our study, no adverse effects were observed with use of ketamine gargles.

Limitations

Although minimal dose of ketamine was used for gargling in this study, it’s minimal systemic absorption cannot be ruled out. Serum ketamine levels were not measured. Systemic analgesic effect of ketamine may have contributed to the outcome of the study. The effects of age, gender, BMI, duration of intubation, size of ET tube, cuff pressure on incidence and severity of POST were not assessed.

Conclusion

Use of 40 mg preservative free Ketamine gargle in 30 ml 0.9% normal saline for 30 seconds, 5 minutes before induction of anaesthesia provides better prophylaxis against post-operative sore throat after endotracheal intubation for various surgeries.

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