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Original Article

Anaesthesia Section

Effect of Preoperative Ketamine Nebulisation on Attenuation of Incidence and Severity of Postoperative Sore Throat, Hoarseness of Voice and Cough: A Randomised Double-blind Study

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ABSTRACT

Introduction: Postoperative Sore Throat (POST) occurs in a majority i.e., upto 62% of patients who undergo endotracheal intubation under general anaesthesia. Ketamine nebulisation has been reported to reduce the incidence and severity of POST.

Aim: To evaluate the effect of ketamine nebulisation on incidence and severity of POST, hoarseness of voice and cough.

Materials and Methods: This prospective, randomised, double-blind study was conducted between September 2020 to February 2021 at J.L.N. Medical College, Ajmer, Rajasthan, India. Total of 100 American Society of Anesthesiologists (ASA) physical status I and II patients were enrolled, and randomly allocated into two groups of 50 each. The patients in Group K (n=50) were nebulised with ketamine (50 mg) with 4 mL normal saline (NS) and in Group S (n=50) were nebulised with 5 mL NS 15 minutes prior to endotracheal intubation. The incidence and severity of POST, hoarseness of voice and cough were assessed just after extubation (0 hour) and thereafter at 2, 4, 6, 12 and 24 hours postoperatively. Haemodynamic parameters {Heart Rate, (HR) Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), and Oxygen Saturation (SpO_2)} were noted before and after nebulisation, and just after intubation. Side-effect profile was also noted. The data from patients was analysed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA, version 21.0 for windows).

Results: Mean age of Group S was 36.22±9.386 years and Group K was 37.40±9.604 years (p-value=0.534). The incidence and severity of POST was significantly lower in patients in Group K at 0 hours (p-value=0.003), at 2 hours (p-value=0.001), at 4 hours (p-value=0.003), at 6 hours (p-value=0.004) and at 12 hours (p-value=0.003), when compared to patients in Group S. The incidence and severity of cough was also significantly lower in patients in Group K at 0 hours, 2 hours, 4 hours and 6 hours (p-value <0.001). Incidence and severity of postoperative hoarseness of voice in Group K was significantly less as compared to Group S at 0 hours, 2 hours, 4 hours and 6 hours (p-value <0.001) and at 12 hours (p-value=0.001). No significant haemodynamic changes (p-value >0.05) and side-effects (p-value=0.727) were noted in both the groups.

Conclusion: Preoperative ketamine nebulisation was found to be effective in reducing the incidence and severity of postoperative sore throat, hoarseness of voice and postoperative cough after general anaesthesia with endotracheal intubation along with no or minimal haemodynamic changes and side-effects.

Keywords: Endotracheal intubation, General anaesthesia, Haemodynamic parameters, N-Methyl D-Aspartate receptor antagonist

INTRODUCTION

Sore throat, hoarseness of voice and cough are common complications following extubation in immediate postoperative period in patients receiving general anaesthesia. Although Postoperative Sore Throat (POST) is usually a self-limiting condition but it may lead to patient discomfort and dissatisfaction [1]. The incidence of POST ranges from 21% to 65% [2,3]. POST can develop due to various perioperative conditions like airway irritation and inflammation, large sized endotracheal tube [4], prolonged duration of surgery [5], excessive movement of endotracheal tube and cuff during patient positioning, airway trauma due to rigid stylet during intubation and prone position [6].

Several non pharmacological methods like appropriate sized endotracheal tubes, gentle laryngoscopy and intubation with minimal duration, using advanced laryngoscopes and maintaining cuff pressure <20 cm of H_2O and pharmacological methods like systemic, topical or aerosolized steroids, gargles or nebulisation with magnesium sulfate, ketamine or local anaesthetics, non steroidal anti-inflammatory drugs and benzydamine gargles or spray on endotracheal tube cuff and oral mucosa have been practised to reduce the incidence and severity of POST [7].

Various factors are responsible for development of POST including pharyngolaryngeal mucosal trauma during laryngoscopy, nasogastric tube insertion or oral suctioning, decreased tracheal mucosal capillary perfusion due to cuff pressure and design, oversized endotracheal tube causes oedema and mucosal lesion. The N-Methyl D-Aspartate (NMDA) receptors are present not only in the central nervous system but also in the peripheral nerves [8,9]. It has been reported that NMDA receptor antagonists like ketamine acts as an antinociceptive and anti-inflammatory agent when given through the peripheral routes [10,11].

Although ketamine has been used as a gargle [12,13] for attenuation of POST by its action on peripheral NMDA receptors in several studies but a limited number of studies has been carried out with nebulised ketamine [13-17]. Preoperative ketamine gargles has an unpleasant taste as well as a larger volume is required for its action so ketamine nebulisation may avoid the drawbacks associated with ketamine gargles [13]. Usually, a fixed dose of ketamine nebulisation (50 mg in 5 mL normal saline) has been used in prevention of POST.

It has been hypothesised that preoperative nebulisation with ketamine would attenuate the incidence and severity of POST, hoarseness of voice and cough. So, the present study was planned to evaluate the role of preoperative ketamine nebulisation on the incidence and severity of POST, hoarseness of voice and cough in patients undergoing various surgeries under general anaesthesia with endotracheal intubation.

MATERIALS AND METHODS

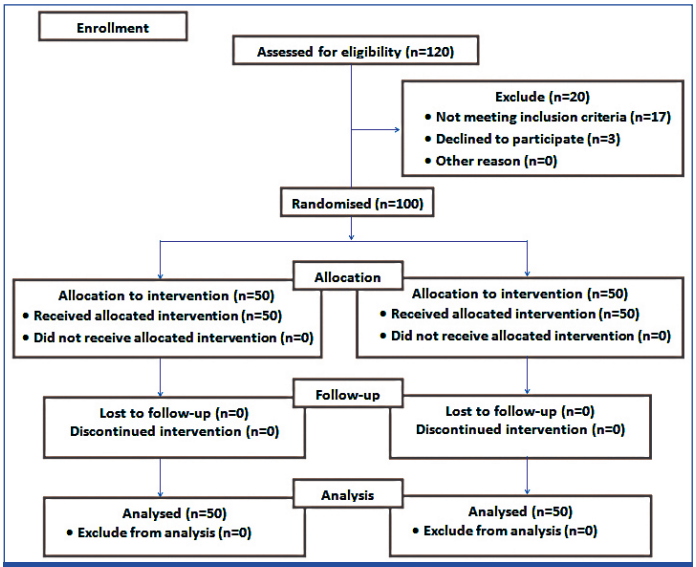
This prospective, randomised, double-blind study was conducted between September 2020 to February 2021 at J.L.N. Medical College, Ajmer, Rajasthan, India. The trial is registered with clinical trials registry-India (CTRI/2020/08/027485) after obtaining the approval from Institutional Ethical Committee (979-Acad/III/MCA/2019).

Sample size calculation: Based on a previous study [16], the sample size was calculated on the basis of assumption of incidence of POST to be 65%. So, an estimated 50% reduction in the incidence of POST with α error of 0.05, 95% confidence interval and 90% power, would require atleast 46 patients in each group to become clinically significant. Finally, sample size was taken as 100 with 50 patients in each group after adding 10% patients for possible dropouts during follow-up.

Inclusion criteria: Patients of either sex, 18-60 years of age belonging to American Society of Anesthesiologists (ASA) physical status I and II undergoing various elective surgeries under general anaesthesia requiring endotracheal intubation were included in this study.

Exclusion criteria: Patients who were not willing to participate in the study, patients allergic to study drug, and history of preoperative sore throat, asthma or chronic obstructive pulmonary disease, patients on chronic medications like non steroidal anti-inflammatory drugs, steroids etc., were excluded from the study. Patients with any psychiatric illness and history of seizures, neurosurgical patients with raised intracranial pressure, patients with history of ischaemic or coronary artery disease and myocardial infarction, pregnant females, patients with anticipated difficult airway and who required >1 attempt during intubation or intubation time >15 seconds and patients posted for oral, head and neck surgeries were also excluded from the study.

The study population was randomly allocated into two groups with 50 patients each, using computer generated table of random numbers. The patients in Group K (n=50) received ketamine nebulisation 50 mg (1 mL) with 4 mL normal saline (total volume=5 mL) and patients in Group S (n=50) received nebulisation with 5 mL normal saline (total volume=5 mL) [Table/Fig-1].



[Table/Fig-1]: CONSORT flow diagram.

Procedure

Preanaesthetic evaluation was done the day before surgery which included thorough history, physical examination and routine investigations. On the day of surgery, after arrival of the patient in preoperative area, baseline vital parameters were recorded. An intravenous (i.v.) cannula was secured and ringer lactate was started. The patients received the study drug via nebulisation mask connected to wall mounted oxygen driven source (8 L, 50 psi) for 15 minutes prior to general anaesthesia. The resident anaesthesiologist who nebulised the patients later did not participate in the further assessment of these patients. The patients were assessed thereafter by another anaesthesiologist. The patients were not aware of group allocation as the study drug was colourless and tasteless (preservative free).

After 10 minutes of nebulisation, the patients were induced for general anaesthesia. All patients were premedicated with glycopyrrolate 0.004 mg/kg i.v. and tramadol 1.5 mg/kg i.v. Preoxygenation was done with 100% Oxygen (O_2) for 3 minutes. Patients were induced with propofol 2 mg/kg i.v. and endotracheal intubation was facilitated with succinylcholine 1.5 mg/kg i.v. Trachea was intubated with an appropriate sized cuffed polyvinyl chloride endotracheal tube followed by cuff inflation using air with no audible leak and bilateral equal air entry in lung fields at peak airway pressure of 20 cm water (H_2O). General anaesthesia was maintained with oxygen (50%) in nitrous oxide (50%), atracurium and sevoflurane (1-1.2 MAC). Ondansetron 4 mg i.v. was given 30 minutes prior to end of surgery.

After completion of surgery, the neuromuscular blockade was reversed with neostigmine 0.05 mg/kg i.v. and glycopyrrolate 0.008 mg/kg i.v. Tracheal extubation was done after the patient become fully conscious following the verbal commands with return of spontaneous respiration and adequate muscle power. Lignocaine 1.5 mg/kg i.v. was given, if patient had excessive coughing during tracheal extubation.

The study parameters (sore throat, hoarseness of voice and cough) were assessed at prenebulisation (baseline before nebulisation), preinduction (after nebulisation just before induction of general anaesthesia), immediate recovery (0 hour after extubation) and postoperative period (at 2, 4, 6, 12 and 24 hours).

After shifting the patient to postoperative ward, sore throat, hoarseness of voice and cough was assessed by the resident anaesthesiologist who was unaware of the group allocation of the patient at 2, 4, 6, 12 and 24 hours postoperatively from the time of extubation. All of these study parameters (POST, postoperative cough and postoperative hoarseness of voice were graded on a four-point scale (0-3) [12].

Postoperative Sore Throat (POST): POST was graded as:

- 0=no sore throat at any time since the operation,
- 1=minimal (patient answered in the affirmative when asked about sore throat),
- 2=moderate (patient complain of sore throat on his/her own), and
- 3=severe (patient is in obvious distress).

Hoarseness of voice: Hoarseness of voice was graded as:

- 0=no complaint of hoarseness at any time since the operation,
- 1=minimal (minimal changes in quality of speech, patient answers in the affirmative only when enquired about),
- 2=moderate (moderate changes in quality of speech of which the patient complains on his/her own), and
- 3=severe (gross changes in the quality of voice perceived by the observer).

Cough: Cough was graded as

- 0=no cough at any time since the operation,
- 1=mild (single cough),
- 2=moderate (more than one episode of unsustained coughing for ≤5 seconds) and
- 3=severe (sustained bout of coughing for >5 seconds).

The various haemodynamic parameters including Heart Rate (HR), Systolic blood pressure (SBP), Diastolic Blood Pressure (SBP), Mean Arterial Pressure (MAP) and oxygen saturation (SpO_2) were recorded at baseline, postnebulisation and postintubation. Various side-effects were also recorded which included tachycardia (HR >100 beats/min), bradycardia (HR <60 beats/min), hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg)), hypotension (SBP <90 mmHg or DBP <60 mmHg), respiratory depression (respiratory rate <12/min), Postoperative Nausea and Vomiting (PONV) and hallucination.

STATISTICAL ANALYSIS

The data from patients was analysed using Statistical Package for the Social Sciences (SPSS) Inc., Chicago, IL, USA, version 21.0 for windows. Kolmogorov-Smirnov test was used for normality of age, weight and haemodynamic variables while the differences in the age and weight was done using an independent student t-test. The various haemodynamic variables between two groups (intergroup) were compared with student t-test and within groups (intragroup) were compared using Analysis of Variance (ANOVA). The differences in the incidence of POST between two groups were compared with Fisher's-test or Chi-square test which ever was applicable. The severity of POST between two groups was compared with Mann-Whitney U test. The p-value <0.05 was considered as statistically significant.

RESULTS

Both groups were comparable in terms of demographic profile i.e., age (p-value=0534), gender (p-value=0.523), ASA physical status (p-value=0.695) and duration of surgery (p-value=0.949) [Table/Fig-2].

Parameters	Group S (n=50)	Group K (n=50)	p-value
Age (years)	36.22±9.386	37.40±9.604	0.534
Gender (M/F)	18/32	15/35	0.523
ASA physical status (I/II)	46/4	47/3	0.695
Duration of surgery (min)	91.90±19.217	92.16±21.242	0.949

[Table/Fig-2]: Demographic profile and duration of surgery in two groups.
Values are expressed as mean±SD and numbers; Chi-square test for categorical data and t-test for numerical data; p-value <0.05 was considered as statistically significant

Both groups showed no statistically significant changes in various haemodynamic or vital parameters i.e., mean HR, mean SBP, mean DBP, mean MAP and mean SpO_2 before and after the nebulisation, and after intubation (p>0.05) [Table/Fig-3].

Parameters	Time	Group S (n=50)	Group K (n=50)	p-value (t-test)
Mean HR (beats/min)	Prenebulisation	82.66±7.631	84.66±8.300	0.213
	Postnebulisation	89.16±8.217	89.30±7.321	0.929
	Postintubation	84.38±8.994	86.78±8.793	0.180
Mean SBP (mmHg)	Prenebulisation	124.04±9.459	126.18±10.694	0.292
	Postnebulisation	126.52±9.474	128.92±7.982	0.174
	Postintubation	125.52±10.706	123.54±9.412	0.328
Mean DBP (mmHg)	Prenebulisation	81.18±4.767	80.92±4.844	0.787
	Postnebulisation	81.54±5.007	82.44±5.418	0.390
	Postintubation	80.56±5.880	80.50±5.148	0.957
Mean MAP (mmHg)	Prenebulisation	95.46±4.879	96.01±5.815	0.612
	Postnebulisation	96.60±5.063	97.93±4.635	0.173
	Postintubation	95.50±6.254	94.85±5.456	0.579
Mean SpO_2 (%)	Prenebulisation	99.78±0.708	99.76±0.657	0.884
	Postnebulisation	99.88±0.385	99.92±0.274	0.551
	Postintubation	100	100	1

[Table/Fig-3]: Haemodynamic parameters.
Values are expressed as mean±SD; p-value <0.05 was considered as statistically significant

The overall incidence of POST in the present study was 34%. A total of 24 (48%) patients in Group S and 10 (20%) patients in Group K had POST at some point of the study. Severity of POST was significantly reduced in Group K compared to Group S, at different time intervals. No patient had severe POST in both groups after 2nd hour, and moderate POST after 4th hour postoperatively [Table/Fig-4].

Similarly, the overall incidence of postoperative hoarseness of voice was 54%. A total of 44 (88%) patients in Group S and 10 (20%) patients in Group K had hoarseness of voice at some point of the study. Severity of hoarseness of voice was significantly reduced in Group K compared to Group S at different time intervals. No patient had hoarseness of voice after 2nd hour postoperatively in Group K [Table/Fig-5].

Time (hours)	Severity of postoperative sore throat	Group S (n=50)		Group K (n=50)		p-value (t-test)
		Incidence as per severity	Total incidence	Incidence as per severity	Total incidence	
0 hours (Postextubation)	Nil	26	24	40	10	0.003
	Mild	12		7		
	Moderate	8		3		
	Severe	4		0		
2 hours	Nil	30	20	44	6	0.001
	Mild	12		6		
	Moderate	6		0		
	Severe	2		0		
4 hours	Nil	34	16	46	4	0.003
	Mild	14		4		
	Moderate	2		0		
	Severe	0		0		
6 hours	Nil	38	12	48	2	0.004
	Mild	11		2		
	Moderate	1		0		
	Severe	0		0		
12 hours	Nil	42	8	50	0	0.003
	Mild	8		0		
	Moderate	0		0		
	Severe	0		0		
24 hours	Nil	48	2	50	0	0.153
	Mild	2		0		
	Moderate	0		0		
	Severe	0		0		
Overall incidence of postoperative sore throat		24		10		0.003

[Table/Fig-4]: Incidence and severity of postoperative sore throat in two groups.
Values are expressed as numbers; p-value <0.05 was considered as statistically significant

Time (hrs)	Severity of post-operative hoarseness	Group S (n=50)		Group K (n=50)		p-value (t-test)
		Incidence as per severity	Total incidence	Incidence as per severity	Total incidence	
0 hours (Postextubation)	Nil	6	44	40	10	<0.001
	Mild	26		10		
	Moderate	17		0		
	Severe	1		0		
2 hours	Nil	18	32	47	3	<0.001
	Mild	20		3		
	Moderate	12		0		
	Severe	0		0		
4 hours	Nil	28	22	50	0	<0.001
	Mild	22		0		
	Moderate	0		0		
	Severe	0		0		
6 hours	Nil	35	15	50	0	<0.001
	Mild	15		0		
	Moderate	0		0		
	Severe	0		0		
12 hours	Nil	40	10	50	0	0.001
	Mild	10		0		
	Moderate	0		0		
	Severe	0		0		

24 hours	Nil	48	2	50	0	0.153
	Mild	2		0		
	Moderate	0		0		
	Severe	0		0		
Overall incidence of postoperative hoarseness of voice			44		10	<0.001

[Table/Fig-5]: Incidence and severity of postoperative hoarseness of voice in two groups.
Values are expressed as numbers; p-value<0.05 was considered as statistically significant

The overall incidence of postoperative severity of cough was 23%; 20 (40%) patients in Group S and 3 (6%) patients in Group K had cough at some point of the study. Severity of cough was significantly reduced in Group K compared to Group S at different time intervals. No patient had cough after 2nd hour postoperatively in Group K [Table/Fig-6].

Time (hours)	Severity of postoperative cough	Group S (n=50)		Group K (n=50)		p-value
		Incidence as per severity	Total incidence	Incidence as per severity	Total incidence	
0 hours (Postextubation)	Nil	30	20	47	3	<0.001
	Mild	15		3		
	Moderate	5		0		
	Severe	0		0		
2 hours	Nil	40	10	47	3	<0.001
	Mild	10		3		
	Moderate	0		0		
	Severe	0		0		
4 hours	Nil	45	5	50	0	<0.001
	Mild	5		0		
	Moderate	0		0		
	Severe	0		0		
6 hours	Nil	47	3	50	0	<0.001
	Mild	3		0		
	Moderate	0		0		
	Severe	0		0		
12 hours	Nil	50	0	50	0	1
	Mild	0		0		
	Moderate	0		0		
	Severe	0		0		
24 hours	Nil	50	0	50	0	1
	Mild	0		0		
	Moderate	0		0		
	Severe	0		0		
Overall incidence of postoperative cough			20		3	<0.001

[Table/Fig-6]: Incidence and severity of postoperative cough in two groups.
Values are expressed as numbers; p-value <0.05 was considered as statistically significant

About side-effects, 2 (4%) patients in Group K and 3 in Group S had PONV, while 2 patients in Group K and 2 in Group S had hypotension but these were statistically insignificant between two groups (p-value >0.05). No other side-effects were noted among two groups [Table/Fig-7].

Adverse events	Group K (n=50)	Group S (n=50)	p-value (Chi-square test)
Tachycardia	0	0	-
Bradycardia	0	0	-
Hypertension	0	0	-
Hypotension	2	2	1
Respiratory depression	0	0	-
PONV	2	3	0.727
Hallucination	0	0	-

[Table/Fig-7]: Adverse effects in two groups.
Values are expressed in numbers; PONV: Postoperative Nausea and Vomiting; p-value <0.05 was considered as statistically significant

DISCUSSION

Although N-Methyl D-Aspartate (NMDA) receptor antagonists have been tried by different authors with variable success [1,7], but a limited number of studies have been done where ketamine was used for nebulisation. Ketamine has been used as a gargle for reducing the incidence and severity of POST. So authors planned a study to evaluate and strengthen the fact that ketamine nebulisation would be effective in reducing the incidence and severity of POST, hoarseness of voice and cough. The overall incidence and severity of POST, hoarseness of voice and cough were found to be significantly reduced in Group K as compared to Group S. A significantly lesser number of patients in Group K had POST (10 versus 24), hoarseness of voice (10 versus 44) and cough (3 versus 20) when compared to patients in Group S.

Ketamine has shown a definitive role in reducing the incidence and severity of POST. The probable mechanism of this effect was due to both topical effect of ketamine nebulisation which has reduced the local inflammation as well as due to peripheral analgesic effect of ketamine. NMDA receptors are found not only in central nervous system but also in the peripheral nerves. Ketamine, an NMDA receptor antagonist has its primary site of action in the central nervous system, and parts of the limbic system while its peripheral effect is suggested via various routes like gargles, nasal or rectal route. NMDA receptors has known to have a role in inflammation and nociception. The available literature showed the topical effect of ketamine via its NMDA-antagonistic action while its anti-inflammatory effect based on animal model data, thus preventing POST [14-18].

Ahuja V et al., and Aditya AK et al., have used 50 mg ketamine nebulisation in study group and 5 mL NS in control group and found that ketamine nebulisation significantly attenuated the incidence and severity of POST, especially during the early postoperative period, with no adverse effects, which is similar to the present study [16,19]. The recovery from general anaesthesia was also found to be faster in ketamine group. Similarly, Mehrotra S et al., evaluated the effects of ketamine, lignocaine and budesonide nebulisation on the incidence on POST [20]. They concluded that sore throat has significantly reduced with ketamine in early postoperative period while lignocaine nebulisation was found to be effective in reducing cough with better long term outcome with budesonide nebulisation. Kumar R compared ketamine nebulisation (50 mg) with ketamine gargle (50 mg) to evaluate their effect on the incidence of POST and found preoperative ketamine nebulisation more effective in reducing POST when compared to ketamine gargle which are in concordance with results of the present study [21].

Jain S and Barasker SK compared the efficacy of isotonic $MgSO_4$ (3 mL), 50 mg ketamine (3 mL) and NS (3 mL) for preoperative nebulisation in patients posted for laparoscopic cholecystectomy [22]. They concluded that incidence of POST was significantly lesser with ketamine nebulisation when compared to $MgSO_4$ nebulisation. Similarly, Reddy M and Fiaz S compared the effectiveness of three different doses (0.5 mg/kg, 1 mg/kg and 1.5 mg/kg) for ketamine nebulisation for 15 minutes duration and 5 minutes prior to intubation [18]. They concluded that the dose of 0.5 mg/kg was found to be less effective than 1 mg/kg and 1.5 mg/kg doses. Charan SD et al., also compared the efficacy of two different doses (25 and 50 mg) of ketamine nebulisation and found both of the doses effective in preventing POST [23]. All the above studies showed reduced incidence and severity of POST with ketamine used by any route and the findings were consistent with the present study results.

Rajan S et al., compared the effect of nebulisation with ketamine 50 mg, $MgSO_4$ 250 mg, $MgSO_4$ 500 mg and NS on attenuating POST, hoarseness of voice and cough in patients undergoing elective abdominal and lower limb surgeries under combined epidural and general anaesthesia [15]. They found a statistically significant decrease in POST at 0, 2, and 4 hour, and postoperative hoarseness at 0 hour with ketamine 50 mg and magnesium sulfate 500 mg. In addition to this, the incidence and severity of sore throat and hoarseness of voice were effectively reduced in the study groups. Although, there was a decrease in the incidence of cough in all the study groups at 0, 2, and 4 hour, but not statistically significant. However, there was no incidence of cough at 12 and 24 hours postextubation in all the four groups. In contrary to this, in the present study the incidence of postoperative cough was significantly reduced in both groups upto 6 hours. Rajkumar G et al., found a significant reduction in hoarseness of voice only at 24 hours, but there was reduction in incidence of it at 0, 2 and 4 hours following ketamine gargle [24]. However, hoarseness of voice was absent in ketamine group after 2 hours postextubation in the present study.

Limitation(s)

The main limitation of the study was serum levels of ketamine were not measured. Experience of anaesthesiologist who did the intubation and the number of attempts were not considered. Further studies need to be carried out to prove and strengthen the role of ketamine nebulisation in reducing POST.

CONCLUSION(S)

Preoperative ketamine nebulisation was found to be effective in reducing both the incidence and severity of POST, hoarseness of voice and cough after general anaesthesia with endotracheal intubation.

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