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NEBULIZATION WITH KETAMINE ATTENUATES POST OPERATIVE SORE THROAT AFTER OROTRACHEAL INTUBATION- A RANDOMIZED, PLACEBO CONTROLLED, SINGLE BLIND CLINICAL TRIAL

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ABSTRACT

BACKGROUND:-Tracheal intubation is a foremost cause of trauma to the airway mucosa, resulting in postoperative sore throat with a reported incidence of 21%-65%, causing hindrance in early discharge in day care surgery.

AIMS:-In this study we have compared the effectiveness of ketamine nebulization with placebo in attenuating postoperative sore throat after orotracheal intubation and to note any adverse reaction if arises.

METHODS:-100 ASA I-II, patients undergoing elective surgery under general anesthesia were randomly divided into 2 groups of 50 each. Group K received Ketamine (50mg in 4 ml saline) nebulization, Group S received saline (5ml) nebulization. Patients were asked to nebulize 15 minutes before induction of anesthesia. Intraoperative Hemodynamic parameters were noted. POST was graded at 0, 2, 8, 12 and 24 hour postoperatively on a four point scale (0-3).

RESULTS:- Post-operative sore throat (POST) occurred more frequently in Group S when, compared to Group K, at 0,2,8 12 and 24hour and significantly more patients suffered severe POST in Group S at 8, 12 and 24 hour compared with Group K.

CONCLUSION:-Ketamine nebulization significantly reduced the incidence and severity of POST.

KEYWORDS : Nebulization, Ketamine, Orotracheal Intubation, Sore Throat

INTRODUCTION

Laryngoscopy and endotracheal intubation marked a new era in the history of anesthesia and has led to the provision of safer anesthesia due to better control of airway and ventilation But the most undesirable outcome associated with endotracheal intubation is the Post-Operative Sore Throat (POST).

POST is recently ranked by American anaesthesiologists as the eighth most important problem of current clinical anaesthesiology. POST following tracheal intubation is due to trauma to the airway mucosa. The reported incidence of POST varies from 21 to 65%[1,2,3,4].

Sore throat has been reported to be one of the most undesirable outcomes in the postoperative period influencing patient satisfaction and the patient's activities after discharge from the hospital[5,6] The frequency of these complications has been directly correlated with the size of the endotracheal tube used during surgery[7] and cuff pressure. It has been clearly demonstrated that the use of a smaller tracheal tube reduces the incidence of sore throat, presumably because of decreased pressure at the tube–mucosal interface[7].

The tracheal-tube cuff has been implicated as a cause of serious sequelae following long-term intubation including tracheal ischaemia, tracheal stenosis and tracheomalacia. So, the cautious recomm endation was made that intra-cuff pressure should be maintained at < 20 mmHg (26 cmH2O).

Loeser and co-workers [8,9,10] extensively investigated the effect of using tracheal tubes with different cuff designs on the incidence of postoperative sore throat, and showed that the high-volume cuffs were associated with a higher incidence of sore throat because of the greater area of cuff–tracheal contact. It was therefore recommended that the ideal cuff should have a diameter slightly less than that of the trachea but should be constructed of material that would allow a 10% increase in diameter over the range of inflating pressure of 20–30 cmH2O.

Postoperative sore throat (POST) is usually self-limiting, but different preoperative pharmacological and non-pharmacological methods may be used as a prophylactic measure against POST. The pharmacological methods includes inhaling beclomethasone; applying lidocaine spray or lidocaine to the ETT; administering aspirin, ketamine, or benzydamine hydrochloride; or gargling with azulene sulfonate[11-15] . The non-pharmacological methods include (as previously discussed) use of smaller size tube, proper monitoring of cuff pressure and use of high volume low pressure cuff.

Here, in this prospective, randomized, controlled study an attempt has been made to observe, assess, and compare the efficacy of use of Nebulized Ketamine in prevention of Post-operative sore throat after endotracheal intubation.

MATERIAL AND METHODS

This prospective, randomized, comparative, single blind study was conducted at a tertiary care hospital in Eastern India over a period of one and half year (January 2016-June 2017) after approval of the Ethical cum Screening Committee. We included 100 patients (determined by power analysis study) in between the age of 18-60 years with American Society of Anesthesiologists (ASA) physical status (PS) I and II, of either sex, weighing between 40 and 60 kg posted for elective short duration (up to 1 hour) surgical procedures under general anesthesia in supine position. Each patient received a written and verbal description of the research protocol and written informed consent was taken from all the patients in their language for inclusion in the study. Exclusion criteria for the study were patients with known cardiovascular, respiratory, renal or hepatic disease, patients with history of pre-operative sore throat, known allergy to study drug, patients with anticipated difficult airway. Eligible patients were randomly allocated using computer generated -randomized test to one of two equal (n=50) groups:

Group K: - Received Ketamine nebulization [1ml (50mg) ketamine + 4ml of saline] for 15 minutes before induction of anaesthesia

Group S: - Received Saline nebulization [5ml] for 15 minutes before induction of anaesthesia

PARAMETERS STUDIED

Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP) were recorded at baseline, after nebulization , intra-operatively at 10 minutes interval and post-operatively.

Assessment of sore throat was done at pre-nebulization, pre induction

and after recovery at 0hr, 2hr, 8hr, 12hr and 24hr postoperatively and graded on a 4 point scale (0-3).

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)

Incidence of side effects like dryness of mouth, cough, nausea, vomiting were also evaluated.

STUDY TECHNIQUE

After approval of the Hospital Ethical cum Screening committee, 100 patients with the above mentioned criteria were selected for the study. On the preceding day of operation, relevant history, preanaesthetic check-up and informed consent of the patient were taken. Patients were advised to fast for 8 hours before surgery. All the patients received tab. Midazolam 7.5mg and tab. Ranitidine 150 mg at the night before operation. After arrival in the operating room, patient's identity and informed consent form were checked and all requisite monitors were attached. Group K patients received ketamine 50mg (1ml) with 4ml of saline nebulization and Group S patients received saline (5ml) nebulization for 15 minutes. Patient were blinded as both preparations were tasteless. Patients were premedicated with inj. Fentanyl (2microgram/kg) 5 min prior to intubation.

All patients received a standardized anesthetic as described-preoxygenation for 3 minutes with gas flow @ 5 liters/minute, followed by induction of anesthesia with inj. Propofol (2mg/kg I.V). Laryngoscopy (using Macintosh Laryngoscope) and intubation with appropriately cuffed endotracheal tube were facilitated with Inj. Vecuronium bromide (0.1mg/kg). Maintenance of anesthesia was done with 40% of O_2 -60% of N_2O, and Isoflurane inhalation 0.6 % MAC. Muscle relaxation was achieved with vecuronium, which was repeated at 25%-30% of the initial dose as per requirement. Ventilation was mechanically controlled and adjusted to control end tidal CO_2 concentration at 30-35 mmHg. At the end of operation residual neuromuscular blockage was antagonized with neostigmine (40 mcg/kg I.V) and glycopyrrolate (0.01mg/kg I.V). Extubation was done only after adequate reversal from general anesthesia judged on clinical basis. For postoperative analgesia, paracetamol (1gm) I.V was administered 6hrly.

STATISTICAL ANALYSIS:

Categorical variables were expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate. Continuous variables were expressed as Mean ± Standard Deviation and compared across the two groups using Mann-Whitney U test. The statistical software SPSS version 20 [Illinois, Chicago: SPSS Inc., 2008] was used for the analysis. A p value < 0.05 was considered as statistically significant and < 0.01 was considered as highly significant.

RESULTS

The two groups were comparable with regards to age, weight, height, BMI and sex. [Table 1,2] . No significant differences were observed between the groups (*p value* > 0.05)

Table 1:- Demographic profile

	Group K		Group S		
	Mean	Standard Deviation	Mean	Standard Deviation	p value
AGE	29.40	6.32	30.14	6.95	0.640
WT	51.56	7.23	52.56	7.93	0.615
HT	150.53	8.13	147.30	8.90	0.157
BMI	23.50	2.79	24.00	3.14	0.755

Table 2: Comparison of sex between the study groups

		Group K		Group S		Total		
		Value	Percentage	Value	Percentage	Value	Percentage	p value
Sex	Male	15	30%	23	46%	38	38%	0.099
	Female	35	70%	27	54%	62	62%	
	Total	50	100%	50	100%	60	100%	

Table 3: Perioperative heart rate (HR) of the patients

	Group K		Group S		
HEART RATE	Mean	Standard deviation	Mean	Standard deviation	p value
BASE LINE	90.24	6.62	89.84	8.80	0.822
After Nebulization	97.06	3.23	97.20	3.61	0.712
After Induction	94.76	6.04	94.26	4.63	0.819
After Intubation	102.04	4.81	99.72	7.52	0.223
10 MIN	86.70	8.11	86.76	7.88	0.912
20 MIN	85.06	7.40	84.56	7.69	0.539
30 MIN	78.04	7.38	77.98	7.61	0.989
40 MIN	76.52	7.64	76.14	7.62	0.656
50 MIN	80.88	10.42	81.14	9.84	0.860
After Extubation	84.90	6.43	84.90	6.23	0.994

From Table 3, the heart rate among the patients in the two groups were comparable with no significant difference throughout the procedure (p>0.05).

Table 4: Perioperative systolic blood pressure (SBP) of the patients

	Group K		Group S		
SBP	Mean	Standard deviation	Mean	Standard deviation	p value
BASE LINE	123.80	16.28	123.20	14.67	0.896
After Nebulization	122.40	16.55	114.53	14.32	0.081
After Induction	119.83	15.48	112.53	16.25	0.099
After Intubation	123.13	15.30	116.33	14.18	0.099
10MIN	124.43	16.98	118.57	13.36	0.088
20MIN	124.50	15.69	117.27	15.89	0.098
30MIN	120.70	16.04	114.83	14.20	0.153
40MIN	123.93	15.42	116.07	15.84	0.096
50MIN	124.20	16.75	115.27	11.75	0.087
After Extubation	124.70	14.76	118.03	7.92	0.050

From Table 4, the systolic blood pressure among the patients in the two groups were comparable with no significant difference throughout the procedure (p>0.05).

Table 5: Perioperative diastolic blood pressure (DBP) of the patient

	Group K		Group S		
DBP	Mean	Standard deviation	Mean	Standard deviation	p value
BASE LINE	77.60	11.00	76.13	8.96	0.618
After Nebulization	77.37	13.56	72.17	10.67	0.144
After Induction	75.70	11.64	71.93	9.57	0.208
After Intubation	77.83	13.86	73.10	10.07	0.163
10 MIN	75.97	10.48	72.50	9.82	0.187
20 MIN	77.53	12.58	71.70	9.18	0.058
30 MIN	78.40	12.61	72.57	10.85	0.093
40 MIN	76.03	11.07	70.20	8.31	0.098
50 MIN	76.70	12.22	71.93	9.67	0.143
After Extubation	77.60	11.05	77.97	7.73	0.885

From Table 5, the diastolic blood pressure among the patients in the two groups were comparable with no significant difference throughout the procedure (p>0.05).

Table 6: Perioperative mean arterial pressure (MAP) of the patient

	Group K		Group S		
MBP	Mean	Standard deviation	Mean	Standard deviation	p value
BASE LINE	93.00	11.39	91.82	9.92	0.713
After Nebulization	92.38	12.20	86.29	10.75	0.072
After Induction	90.41	11.32	85.47	10.52	0.105
After Intubation	92.93	12.61	87.84	9.59	0.098
10 MIN	92.12	11.10	87.52	9.08	0.098
20 MIN	93.19	11.67	88.22	10.08	0.099
30 MIN	92.50	11.44	86.66	10.81	0.077
40 MIN	92.00	10.28	89.82	10.33	0.102
50 MIN	92.53	12.22	88.04	8.83	0.097
After Extubation	93.30	11.10	91.32	6.96	0.426

From Table 6, the mean arterial pressure among the patients in the two groups were comparable with no significant difference throughout the procedure (p>0.05).

Table 7: Post-operative sore throat (POST) score at 0 hours

		Groups		Total		
		Group K	Group S		p Value	Significance
POST_0	0	45(90%)	34(68%)	79(79%)	0.031	Significant
	1	3(6%)	10(20%)	13(13%)		
	2	2(4%)	6(12%)	8(8%)		
Total		50(100%)	50(100%)	100(100%)		

Table 8: Post-operative sore throat (POST) score at 2 hours

		Groups		Total		
		Group K	Group S		p Value	Significance
POST_2	0	44(88%)	31(62%)	75(75%)	0.008	Significant
	1	5(10%)	12(24%)	17(17%)		
	2	1(2%)	7(14%)	8(8%)		
Total		50(100%)	50(100%)	100(100%)		

Table 9: Post-operative sore throat (POST) score at 8 hours

		Groups		Total		
		Group K	Group S		p Value	Significance
POST_8	0	47(94%)	34(68%)	81(81%)	0.002	Significant
	1	3(6%)	7(14%)	10(10%)		
	2	0(0%)	2(4%)	2(2%)		
	3	0(0%)	7(14%)	7(7%)		
Total		50(100%)	50(100%)	100(100%)		

Table 10: Post-operative sore throat (POST) score at 12 hours

		Groups		Total		
		Group K	Group S		p Value	Significance
POST_12	0	48(96%)	34(68%)	82(82%)	0.001	Significant
	1	2(4%)	7(14%)	9(9%)		
	2	0(0%)	2(4%)	2(2%)		
	3	0(0%)	7(14%)	7(7%)		
Total		50(100%)	50(100%)	100(100%)		

Table 11: Post-operative sore throat (POST) score at 24 hours

		Groups		Total		
		Group K	Group S		p Value	Significance
POST_24	0	48(96%)	32(64%)	80(80%)	0.000	Significant
	1	2(4%)	7(14%)	9(9%)		
	2	0(0%)	2(4%)	2(2%)		
	3	0(0%)	9(18%)	9(9%)		
Total		50(100%)	50(100%)	100(100%)		

From Table 7,8,9,10,11 , the incidence of post-operative sore throat among the patients in the two groups were comparable with significant difference throughout the duration ($p<0.05$).

Table 12. Comparison of adverse effects among the study groups

		Groups		Total		
		Group K	Group S		p Value	Significance
Adverse effects	Dryness of mouth	1(2%)	0(0%)	1(1%)	1.000	Not Significant
	None	49(98%)	50(100%)	99(99%)		
Total		50(100%)	50(100%)	100(100%)		

From Table 12, 1(2%) patient complained of dryness of mouth in Ketamine group. No other complications were seen in this study.

DISCUSSION

In an anaesthetized patient, the free airway is of vital importance, and this is often maintained by use of an endotracheal tube (ETT).The purpose of an endotracheal intubation is to ensure a secure airway and provide an opportunity for positive pressure ventilation and minimal risk of aspiration[16].If an airway complication occurs, it is usually a consequence of anaesthesia itself [17]. Apart from injury to the teeth, the most common complications of endotracheal intubation are post-operative sore throat (POST) and postoperative hoarseness (PH) [18-20].

Post-operative sore throat, while usually self-limiting, was rated by patients as one of the top 10 most undesirable postoperative outcomes[6]. The etiology is probably one or more of the following: mechanical injury during intubation, damage to mucosa due to the pressure from the endotracheal (ET) tube cuff, and dehydration of the mucosa[21].

The duration of time a patient stays in the post anesthesia care unit, or potentially the facility, because of POST increases the cost of care. Patients with POST had a 14-minute longer stay in the post anesthesia care unit and a 25-minute longer stay in the ambulatory care unit, and were discharged 51 minutes later from the facility compared with those who did not complain of POST[5]. Reducing the severity and incidence of POST should decrease the length of stay and cost of care, and improve patient satisfaction.

In this prospective, randomized, controlled study we have evaluated the role of ketamine nebulization on incidence and severity of POST. We observed reduction in the incidence and severity of POST at 0hr, 2hr, 8hr, 12hr and 24hr, in patients receiving ketamine nebulization as compared to control group, following GA with tracheal intubation lasting for up to 1 h.

In the present study, the incidence of POST at 8, 12 and 24hr was significantly reduced, and the attenuation of severity of POST occurred in the ketamine group. 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.[12,22,23] Literature supports the topical effect of ketamine via its NMDA-antagonistic action and anti-inflammatory effect based on animal model data.[22,23,24,25] 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.[12,22,23] Experimental animal studies have shown a protective effect on airway inflammatory injury with ketamine nebulisation.[26]

The primary outcome of the study was the incidence of POST at 2 hr 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.[12,22-28] 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.[27] Ketamine gargle has been found to be effective in reducing the incidence and severity of POST due to its anti-inflammatory effects.[25] 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.[28] 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.

In respect to the adverse effects only dryness of mouth was noted in one patient out of 50 in ketamine group which was not statistically significant.

In relation to the hemodynamic parameters there was no significant changes in respect to SBP, DBP, MBP, HR, in either of the two groups.
In our study patients were nebulized 15 minutes before induction of anesthesia. It was found that pneumatic nebulization method produced 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 anesthesiologists 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 H2O.

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.

CONCLUSION

In this prospective, randomized, single blind comparative clinical study we found that the use of pre-operative ketamine nebulization reduced the incidence and severity of POST during early post-operative period in patients receiving GA with tracheal intubation. Dryness of mouth was the only side effect noticed in patients receiving ketamine nebulization. But this side effect occurred only in one patient and did not cause any harm to the patient, and also corrected spontaneously.

So from these observations we can conclude that Nebulization with ketamine decreases the incidence and severity of post-operative sore throat .Thus this technique adds to the armamentarium of the anesthetist in management of the 'little big problem' of POST.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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