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Research Article

Preoperative Nebulization of Ketamine and Dexmedetomidine for Reduction in Postoperative Sore Throat: A Comparative Double- Blind Study

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ABSTRACT

Background: One of the most prevalent procedures involving general anaesthesia (GA) is endotracheal intubation, which can lead to a variety of airway complications. Patients undergoing GA with tracheal intubation may experience a common complication, known as postoperative sore throat (POST). This study was undertaken to evaluate and compare the efficacy between nebulized ketamine and dexmedetomidine administered preoperatively in alleviating POST.

Methods: Patients were randomized into two groups with 151 patients in each group. Group-K patients were nebulized with ketamine 50mg (1ml) with 3ml normal saline, while Group-D patients were nebulized with dexmedetomidine 50mcg (0.5ml) with 3.5ml normal saline, preoperatively. GA was administered 15 min post-nebulization. POST was graded at 4,6,12 and 24h after extubation; on a four-point scale (0-3). The statistical analysis was performed using statistical package for social science (SPSS) software version 17.0.

Results: In the present study, the overall incidence of POST was 32.5%. POST was experienced by 39 patients (25.8%) in ketamine and 59 patients (39.1%) in dexmedetomidine group (P value=0.014) at 4h, following extubation. Significantly higher incidence of POST in dexmedetomidine group was noticed as compared to ketamine group (P value <0.05). But, at 6h, 12h and 24h, the difference was not statistically significant between the two groups. A significantly larger percentage of cases in dexmedetomidine group had more severe POST than in ketamine group, at 4h following extubation (p-value <0.05). There was no significant rise in systolic and diastolic blood pressure in either groups. However ketamine group had a significantly higher mean heart rate after extubation compared to dexmedetomidine group.

Conclusion: Ketamine nebulization significantly decreases the incidence and severity of post operative sore throat, during the early postoperative period with minimum hemodynamic changes.

Introduction

For general anesthesia, laryngoscopy and endotracheal intubation is the gold standard anesthetic technique for elective surgeries. Despite rapid advancements in general anesthesia techniques, such as, machines, equipments, monitoring technology and introduction of competency- based training, sore throat as a secondary side effect after tracheal intubation persists in patients undergoing elective surgery. Postoperative sore throat (POST) ranks second among the most common side effects of surgery, apart from nausea and vomiting [1]. The overall incidence of POST after general anesthesia ranges from 20% to 74% [2]. The

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epithelial and mucosal cells damage and compromised capillary perfusion of the vocal cords due to endotracheal cuff pressure during intubation are the main causes of POST [3].

In recent years, various studies have been undertaken to find out the factors that cause POST. The patient related factors include the age, sex, and smoking. The other factors related to intubation, which are attributed to POST include, intubation technique, duration, tube size, intracuff pressure, cuff design, intraoperative tube movement and suctioning. The postoperative pain, including sore throat, increases analgesic use [4].

In order to overcome the patient dissatisfaction owing to POST, number of pharmacological agents have been administered via different routes, such as through gargling, intravenously or even through nebulization therapy. Some of the pharmaceuticals used to treat POST, include aerosolized drugs, such as, corticosteroids, ketamine, magnesium, lidocaine, non-steroidal anti-inflammatory drugs (NSAIDs) etc. [5].

As an innovative premedication technique, nebulization increases drug absorption via the airway mucosal surfaces, has better patient acceptability and improves clinical efficacy, all of which contribute to a decrease in occurrence and severity of POST.

Ketamine and dexmedetomidine have been administered preoperatively mainly through gargling, intravenously and through nebulization to decrease the incidence and severity of POST. However, ketamine has an extremely unpleasant taste, requires large volume, and may cause aspiration when used as gargles. Hence, nebulization is an effective and safe route of administration of ketamine and dexmedetomidine for reducing POST, as compared to gargling and intravenous routes.

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptors antagonist is involved in anti-nociceptive and anti-inflammatory cascade by reducing NFkβ activity and TNFα, and hence is effective in preventing sore throat [6].

Dexmedetomidine has analgesic and sedative effects, being selective ∝– 2-adrenergic receptor agonist. It has been used to reduce the anesthetic requirements in clinical settings and also provides stable hemodynamics [7]. Both nebulized dexmedetomidine and ketamine have bioavailability of approximately 65% through the nasal mucosa and 82% through the buccal mucosa [8-9].

The role of ketamine and dexmedetomidine in attenuation of POST including their effect on change in hemodynamic parameters have been studied extensively. However very few studies have compared them in nebulized form.

Therefore, the present study includes the comparison of the efficacy between nebulized ketamine and dexmedetomidine administered preoperatively, in alleviating POST and their effect on the change in hemodynamic parameters for patients undergoing elective surgery following general anesthesia with endotracheal intubation.

Methods

The present investigation was a prospective, randomized, double-blind and comparative study, carried out during the period between June 2022 and January 2024, at tertiary care Centre. The institutional ethics committee approval was obtained (BVDUMC / IEF/81) along with approval from CTRI (CTRI/2023/06/05 4022) prior to the commencement of the study. After receiving written informed consent from participating patients, 302 patients between the age group of 18 and 60, who were scheduled for elective surgeries under general anesthesia and intubation, were enrolled for the study.

The sample size has been calculated by the formula detailed below [10].

Sample size(n)=

$$\frac{\left[Z_{(1-\alpha/2)}+Z_{(1-\beta)}\right]^2 \times [P_1(100-P_1)+P_2(100-P_2)]}{d^2} \quad (1)$$

P1: Proportion / prevalence in the 1st group from reference study.

P2: Proportion / prevalence in the 2nd group from reference study.

d: allowable error (absolute precision) or difference between two proportions from reference study (P1-P2). The level of significance was taken at 0.05 or 5% and the standard normal value for 80% power was approximately

0.84. The random allocation sequence was generated by chit method before registration of participants. The enrolled study participants were randomized equally into two groups (151 in each group) as follows:

Group K - Nebulized with ketamine 1.0 ml and 3.0ml normal saline.

Group D - Nebulized with dexmedetomidine 0.5ml and 3.5ml normal saline.

Inclusion criteria

Patients between age group of 18 and 60 years. Patients of either sex. Patients satisfying ASA status I and II.

Exclusion criteria

- Patients with history of prior sore throat.
- Patients with chronic usage of steroids or non-steroidal anti- inflammatory drugs.
- Patients with chronic obstructive pulmonary disease, Asthma and Hypertension.
- Patients requiring more than 2 attempts of intubation. Pregnant women.
- Patients on β blockers.
- Patients with nasogastric tube and Patients requiring throat pack.
- Patients with breast feeding.

- Patients with anticipated difficult airway. Patients with known allergy to study drug

Pre anesthetic checkup (PAC)

The pre-anaesthetic evaluation was undertaken one day prior to surgery. Patients meeting our inclusion criteria were enrolled. The procedure of general anesthesia was explained to the patient and written informed consent was obtained. Patient were kept nil by mouth as per nil per oral (NPO) guidelines.

Methods

The nebulization procedure was carried out in the preoperative room. The solutions of nebulized drugs (ketamine or dexmedetomidine) with normal saline as mentioned above were prepared by the anesthesia assistant, who had received the drug from the research supervisor. The investigator and the patient were unaware about the actual drug, as both the solutions of nebulized drugs were colorless, odorless and of equal volume. Then, the prepared solution was placed in the nebulizer cup. An electrical compressor nebulizer was used, which produces fine mist. Nebulization was carried out for 15 minutes. General Anesthesia was administered 15 minutes after completing the nebulization. Standard protocol of GA was followed in both groups as follows: Before induction of anesthesia, IV line was secured and multi parameters which include Pulse Rate, Blood Pressure, SpO2, ET CO2 were recorded for each patient and throughout the procedure cuff pressure was monitored.

Premedication– Injection Glycopyrrolate 0.2mg IV + inj. Ondansetron 4 mg IV.

Preinduction– Injection Midazolam 1mg IV + Injection Fentanyl 1-2mcg/kg.

Induction– Injection propofol 2-2.5 mg/kg, titrated to effect

Intubation- Under the effect of muscle relaxant Injection. Atracurium 0.5mg/kg IV, portex cuffed ETT No.7 for females and No.8 for Males was inserted under vision. The cuff pressure was maintained between 20-30cm of H2O and monitored by cuff pressure manometer, every hourly.

Maintenance – Injection Atracurium + IPPV close circuit

+ Sevoflurane.

Extubation– Immediately after the procedure, the patient was given 0.05 mg/kg of neostigmine and 0.01 mg/kg of glycopyrrolate. The patient was reversed adequately and extubated as per clinical criteria.

After surgery, patients were shifted to postoperative care unit (PACU).

Sore throat symptoms were evaluated at four, six, twelve, and twenty-four hours following extubation, on a four-point scale as follows:

Grade- 0 no sore throat,

Grade- 1 mild sore throat (i.e., only complains when asked),

Grade- 2 moderate sore throat (i.e., complains even when not asked),

Grade- 3 severe sore throat (i.e., changes in voice or pain in the throat).

Statistical analysis

At the end of the study, statistical analysis was done using the SPSS software unit's interpretation and graphical representation of the available data. In order to compare the actual results with the predicted ones, a chi-square test is employed. The independent sample 't' test is performed to check whether the associated population means are significantly different or not. A result is considered statistically significant, when the P value obtained from the test is less than 0.05.

Results

The total number of patients screened for study were 317. The number of patients failed to meet the inclusion criteria were found to be 15. Hence, 151 patients were allocated to each study group, as detailed below (Figure 1).

The inter-group comparison of demographic characteristics, BMI, and surgery duration of were analysed. No significant differences were noticed between the two study groups, relating to age, BMI, and duration of surgery (Table 1).

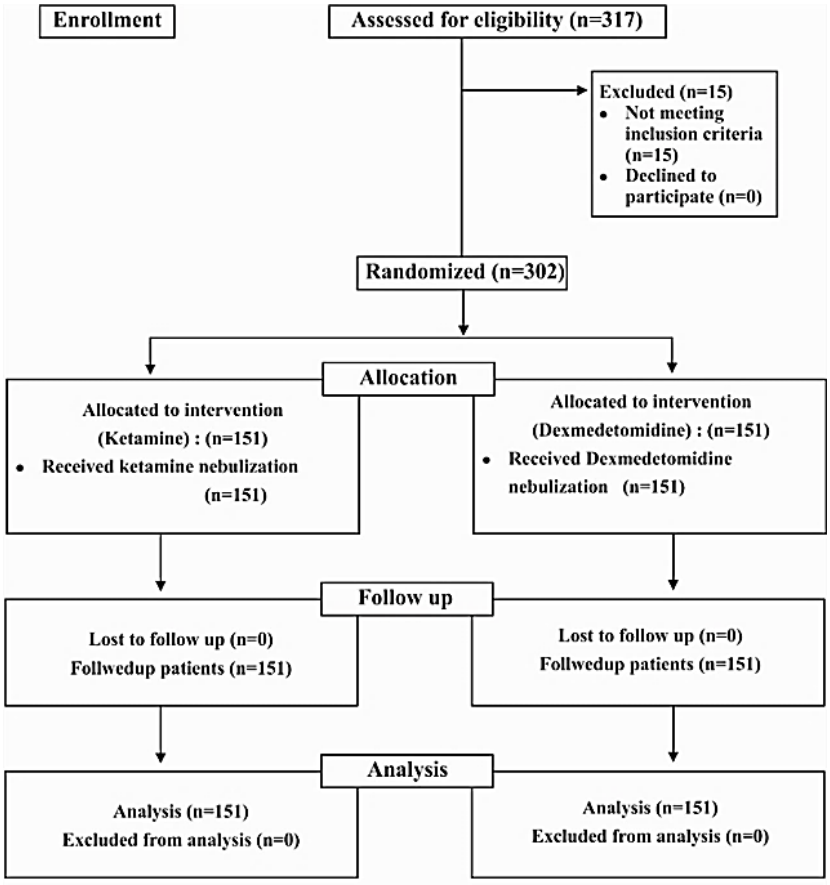

Figure 1-Consort flow diagram of patients involved.

Table 1- Inter-group comparison of demographic characteristics including BMI and mean duration of surgery.

		Group K (n=151)	Group D (n=151)	P value
Age (years) Mean±		37.13± 12.84	37.81± 12.39	0.639
Sex	Male n (%)	93 (61.6%)	77 (51.0%)	0.639
	Female n (%)	58 (38.4%)	74 (49.0%)	
BMI (kg/m^2) Mean ± SD		22.40± 2.58	22.45± 2.75	0.868
Duration of Surgery (h) Mean ±SD		2.84 ± 0.58	2.93 ± 0.58	0.218

In the present study, the overall incidence of POST was 32.5%. At the 4 h post extubation time interval, there was a noticeable higher incidence of POST in group-D (39.1%) compared to group-K (25.8%), in the cases that were examined. No statistically significant difference was found, when comparing the distribution of POST incidence at 6 h, 12 h and 24 h post extubation time interval, between the two study groups (all P value>0.05) (Table 2).

Table 2- Inter-group comparison of incidence of POST

POST		Group K (n=151)		Group D (n=151)		P value
		n	%	n	%	
4h	Present	39	25.8	59	39.1	0.014*
	Absent	112	74.2	92	60.9	
6h	Present	19	12.6	28	18.5	0.153
	Absent	132	87.4	123	81.5	
12h	Present	2	1.3	5	3.3	0.448
	Absent	149	98.7	146	96.7	
24h	Present	0	0	3	2.0	0.248
	Absent	151	100	148	98	

The inter-group comparison of grades of severity of POST were analysed (Table 3). It is observed that, at 4 h post-extubation time interval, a significant larger percentage of cases in group-D had more severe POST than cases in group-K (value,0.05). But, no statistically significant of POST between the study groups were noticed at 6 h, 12 h and 24 h time intervals (P value>0.05 in each case).

Base line heart rate was recorded in both the groups, Group K and Group D before intubation. After intubation there were no significant change in mean heart rate between the two groups, but group K had a significantly higher distribution of mean heart rate after extubation compared to Group D (P value<0.05) among the cases studied (Figure 2).

Table 3- Inter-group comparison of grades of severity of POST

Grades of POST		Group K (n=151)		Group D (n=151)		P value
		n	%	n	%	
4h	No sore throat	112	74.2	92	60.9	0.031*
	Mild	32	21.2	47	31.1	
	Moderate	7	4.6	8	5.3	
	Severe	0	0	4	2.6	
6h	No sore throat	132	87.4	123	81.5	0.311
	Mild	16	10.6	23	15.2	
	Moderate	3	2	3	2	
	Severe	0	0	2	1.3	
12h	No sore throat	149	98.7	146	96.7	0.387
	Mild	2	1.3	2	1.3	
	Moderate	0	0	2	1.3	
	Severe	0	0	1	0.7	
24h	No sore throat	151	100	148	98	0.248
	Mild	0	0	3	2	
	Moderate	0	0	0	0	
	Severe	0	0	0	0	

The distribution of mean systolic BP and diastolic BP among the two groups of patients did not differ appreciably before intubation, after intubation and after extubation (P value> 0.05) respectively in each case (Figure 3,4).

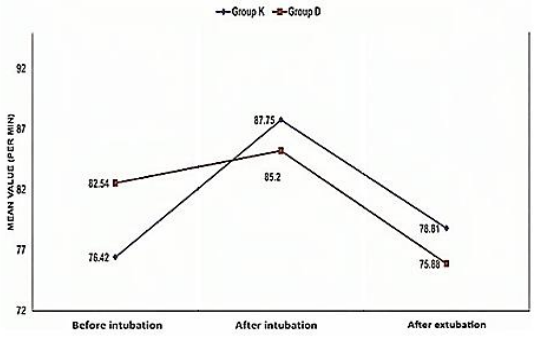

Figure 2- Inter-group distribution of mean heart rate.

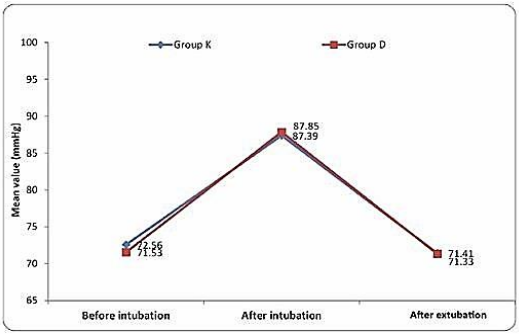

Figure 3- Inter-group Distribution of mean systolic BP.

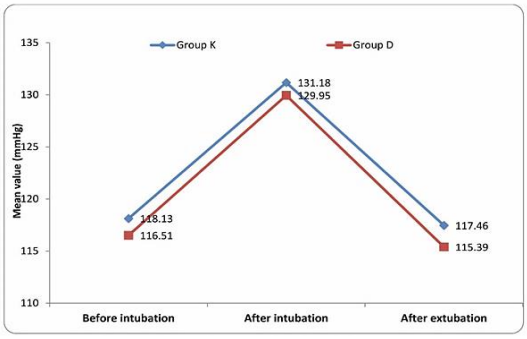

Figure 4- Inter-Group distribution of mean diastolic BP

Discussion

POST is considered as one of the most common complications developing in patients undergoing surgery under general anaesthesia with endotracheal intubation. The cause of POST includes injury to airway mucosa during endotracheal intubation and extubation, in addition to the pressure on the mucosa exerted by the inflated endotracheal tube cuff. The effect of various pharmacological interventions and non-pharmacological methods on the incidence of POST have been studied by different researchers. The non-pharmacological methods studied to reduce incidence POST includes ETT size, ETT cuff pressure etc. It was observed that, ETT of 6.0-7.5mm internal diameter (ID) for female and 7.0-8.0mm (ID) for male patients reduces POST significantly as compared to larger size ETT [11]. Therefore, we have used No.7 ETT for females and No. 8 ETT for males in our study. EL-Boghdadly et al. reported that the incidence of POST reduced significantly, when 6.0mm ID of ETT was used instead of 7.0mm ID. The decrease of 1mm ID of ETT size remarkably decreases the incidence of POST [12].

Periodical monitoring of cuff pressure is paramount, as over and under inflation of the tracheal tube cuff are associated with further complications. The ideal range of ETT cuff pressure should be between 20-30cm of H2O. An overinflated ETT cuff exerts excess pressure on the trachea which may lead to tracheal wall ischemia and necrosis, while inadequate cuff inflation increases the risk of micro-aspiration, aspiration pneumonitis and pneumonia as well as self extubation. [13]. The ETT cuff inflated with 2% lignocaine reduces the occurrence and severity of POST, as it acts as local anesthetic and reduces inflammation of the trachea [14]. The various pharmacological agents studied to reduce incidence of POST are corticosteroids, lidocaine, NSAIDs and NMDA receptor antagonists. [5]. The pharmacological drugs are administered through gargling, intravenous and nebulization in different studies. In previous studies, stability of hemodynamic parameters was noticed during the intraoperative period by nebulization route as compared to intravenous route [15]. Therefore, nebulization route is considered as safe and effective. Singla A et.al. also reported that, the hemodynamic parameters are more stable with nebulized dexmedetomidine compared to intravenous administration, before and after intubation [16].

The overall incidence of POST was found to be 32. 5% in our study. We monitored the incidence and severity of POST in the study participants at 4, 6, 12, and 24 hours following extubation. The incidence of POST was determined to be 25.8% in Group K and 39.1% in Group D at 4 hours postoperatively after the extubation. Which shows that patients nebulized with dexmedetomidine experienced significantly more POST than those nebulized with ketamine (P-Value < 0.05).

The distribution of incidence of POST at 6, 12, and 24 hours post-operatively did not reveal any statistically significant difference between the two groups.

In a study by D. Thomas et al, overall incidence of POST was 17% [2]. They have reported the incidence of POST being 14.3% in ketamine and 20.4% in dexmedetomidine respectively, which is identical with our study.

Similarly, Jandial et al. evaluated nebulized ketamine and nebulized dexmedetomidine to reduce the incidence of POST and concluded that at 2-hour interval, the ketamine group had a lower incidence of POST (14.58%) compared to the dexmedetomidine group (16.66%) [17], which is also similar to our study.

We also studied the inter-group comparison of grades of severity of POST at different time intervals.

We found that the incidence of mild POST in group K was 21.2% while in group D it was 31.1% at 4hrs interval. Similarly, the incidence of moderate POST in group K was 4.6% and in group D it was 5.3% at 4hrs respectively. However, we did not come across severe grade of POST in group K, but 2.6% patients in group D experienced severe POST at 4hrs (P value=0.031). Thus, at the 4-hours post-operative time interval, there was statistically significant difference in the distribution of POST severity grades between Group-D and Group-K. At 6, 12, and 24 h marks, however, there was no statistically significant difference in POST severity between the two groups (all P values > 0.05). Ittoop A L et.al. investigated the impact of nebulized ketamine and dexmedetomidine on POST and compared the hemodynamic parameters [18]. They have concluded that, hemodynamic parameters, such as, HR, SBP, DBP did not change significantly between the group of patients at any point of time, which is in line with our findings.

Limitations

In our study we have not included pediatric patients undergoing surgery under GA, considering the anatomical and physiological differences from the adult airway and a need for different study protocol as per the study population.

We could not estimate the contribution of systemically absorbed drug to the study findings as we have not measured the serum levels of the nebulized drugs. The analgesia could partly be due to other systemic analgesics and anesthetics drugs administered perioperatively; however, they were administered equally in both groups and are unlikely to affect the difference in the findings observed in the two groups. The use of polyurethane ETT instead of PVC cuffed tube and their effect on POST have not been investigated as it was not a part of study protocol.

Conclusion

Nebulisation is a safe and effective route of administration, with good patient acceptability. Preoperative nebulization of ketamine and dexmedetomidine nebulization is equally effective in decreasing the incidence and severity of POST, with minimum hemodynamic disturbances. However, at 4hrs nebulized ketamine has shown significant reduction in POST. Therefore, ketamine can be considered as a better alternative to dexmedetomidine in reducing POST.

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