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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 anesthesia (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). We conducted this study to assess and compare the effectiveness of preoperatively administered nebulized ketamine and dexmedetomidine in alleviating POST.

Methods: We randomly divided the patients into two groups, each containing 151 patients. Group-K patients were nebulized with 50 mg (1 ml) with 3 ml normal saline, while Group-D patients were nebulized with dexmedetomidine 50 mcg (0.5 ml) with 3.5 ml normal saline, preoperatively. GA was administered 15 min post-nebulization. POST was graded at 4, 6, 12, and 24 h after extubation on a four-point scale (0-3). The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 17.0.

Results: In the present study, the overall incidence of POST was 32.5%. among which 39 patients (25.8%) in the ketamine group and 59 patients (39.1%) in the dexmedetomidine group experienced POST at 4h, following extubation (P value=0.014). A significantly higher incidence of POST in the dexmedetomidine group was noticed as compared to the 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 the dexmedetomidine group had more severe POST than in the ketamine group, at 4h following extubation (p-value <0.05). There was no significant rise in systolic and diastolic blood pressure in either group. However, the ketamine group had a significantly higher mean heart rate after extubation compared to the dexmedetomidine group.

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

Introduction

For general anesthesia, laryngoscopy and endotracheal intubation are the gold standard anesthetic techniques for elective surgeries. Despite rapid advancements in general anesthesia techniques, such as machines, equipment, monitoring technology, and the 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,

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apart from nausea and vomiting [1]. The overall incidence of POST after general anesthesia ranges from 20% to 74% [2]. The epithelial and mucosal cell damage and compromised capillary perfusion of the vocal cords due to endotracheal cuff pressure during intubation are the main causes of POST [3].

Researchers have conducted a number of studies in recent years to identify 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, a 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].

Nebulization is a new way to give medicine by inhaling the mist produced by the nebulizer. It improves clinical efficacy, makes the drug more bioavailable through the mucosal surfaces of the airways, and is more acceptable by patients. All of these factors help lower the number and severity of POST episodes.

Preoperatively, we primarily administer ketamine and dexmedetomidine through gargling, intravenously, and nebulization to reduce the incidence and severity of POST. However, ketamine has an extremely unpleasant taste, requires a large volume, and may cause aspiration when used as gargles. Therefore, nebulization is a better and safer way to give ketamine and dexmedetomidine to lower POST than gargling or giving them through an IV.

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, is involved in the 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 a selective α–2-adrenergic receptor agonist. Clinical settings have used it to reduce anesthetic requirements and to provide stable hemodynamics [7]. Both nebulized dexmedetomidine and ketamine have a bioavailability of approximately 65% through the nasal mucosa and 82% through the buccal mucosa [8-9].

The role of ketamine and dexmedetomidine in the attenuation of POST, including their effect on changes in hemodynamic parameters, has 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 a tertiary care Centre. Prior to the commencement of the study, we obtained approval from the institutional ethics committee (BVDUMC / IEF/81) and CTRI (CTRI/2023/06/05 4022). 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 formula below [10] has calculated the sample size.

sample size(n)=

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

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

P2: Proportion/prevalence in the second group from the 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 the 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 3.0 ml normal saline.

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

Inclusion criteria

The patients range in age from 18 to 60 years. Patients can be of either gender. These patients meet the criteria for ASA status I and II.

Exclusion criteria

- Patients with a 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 are being treated.
- Patients requiring more than two attempts at intubation. Pregnant women.
- Patients on β blockers.
- Patients with nasogastric tubes and patients requiring throat packs.

- Patients who are breastfeeding are currently receiving care.
- Patients with anticipated difficult airway.
- Patients with known allergies to the studied drug

Pre-anesthetic checkup (PAC)

We conducted the pre-anesthetic evaluation one day before surgery. We enrolled patients who met our inclusion criteria. We explained the general anesthesia procedure to the patient and obtained their written informed consent. As per the nil by mouth (NPO) guidelines, we kept the patients nil by mouth.

Methods

The nebulization procedure was carried out in the preoperative room. As was already said, the anesthesia assistant mixed nebulized drugs (ketamine or dexmedetomidine) with normal saline to make the solutions. The drug came from the research supervisor. The investigator and the patient were unaware of the actual drug, as both the solutions of nebulized drugs were colorless, odorless, and of equal volume. We then placed the prepared solution in the nebulizer cup. We used an electrical compressor nebulizer, which produces fine mist. Nebulization was carried out for 15 minutes. General anesthesia was administered 15 minutes after completing the nebulization. Both groups adhered to the standard GA protocol. Before induction of anesthesia, the IV line was secured, and multiple parameters, which include pulse rate, blood pressure, SpO_2, and ET CO_2, were recorded for each patient, and throughout the procedure, cuff pressure was monitored.

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

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

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

The patient underwent intubation while receiving a muscle relaxant injection. A portex cuffed ETT No. 7 for females and No. 8 for males was inserted under vision. The cuff pressure was maintained between 20-30 cm of H_2O and monitored by a cuff pressure manometer every hour.

Maintenance—Injection Atracurium + IPPV close circuit

+ Sevoflurane.

Following the procedure, the patient received 0.05 mg/kg of neostigmine and 0.01 mg/kg of glycopyrrolate for extubation. The patient was reversed adequately and extubated as per clinical criteria.

Following surgery, the postoperative care unit (P) received the patients.

We evaluated sore throat symptoms on a four-point scale at four, six, twelve, and twenty-four hours after extubation.

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, we performed statistical analysis using the SPSS software unit. 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. We perform the independent sample 't' test to determine 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 the study was 317. The number of patients who failed to meet the inclusion criteria was found to be 15. Hence, 151 patients were allocated to each study group, as detailed below (Figure 1).

We analyzed the inter-group comparison of demographic characteristics, BMI, and surgery duration. We found no significant differences in age, BMI, and surgery duration between the two study groups (Table 1).

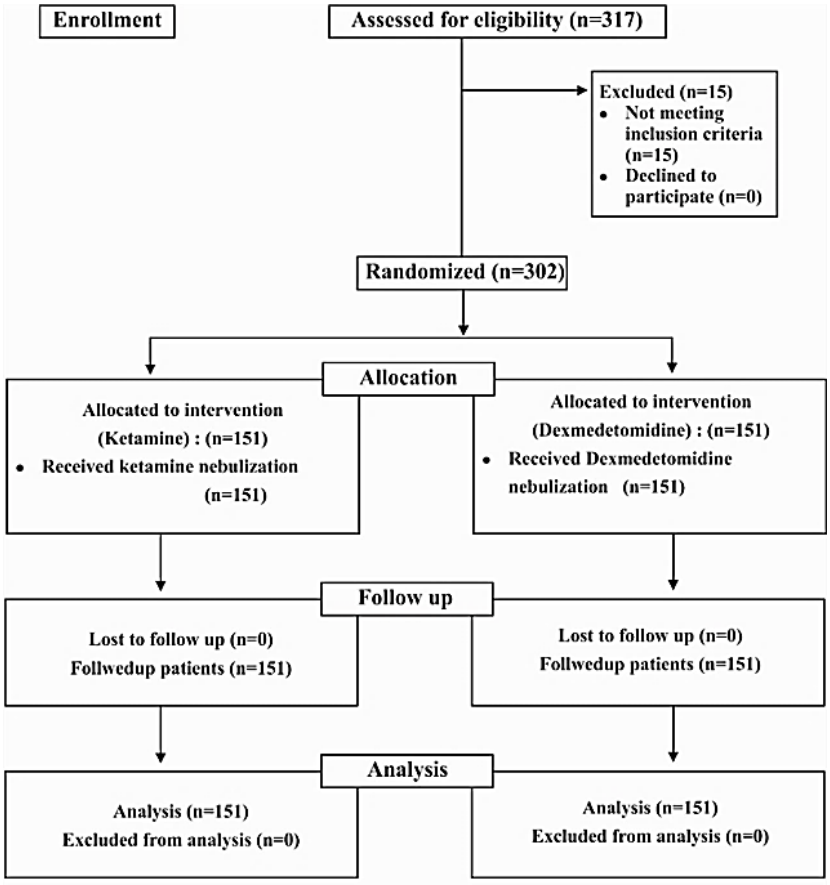

Figure 1-Consort flow diagram of patients involved.

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 noticeably higher incidence of POST in group-D (39.1%) compared to group-K (25.8%) in the cases that were examined. When the rates of POST were compared between the two study groups 6 hours, 12 hours, and 24 hours after extubation, there was no statistically significant difference (all P values > 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	

We analyzed the inter-group comparison of POST severity grades (Table 3). It is observed that, at the 4 h post-extubation time interval, a significantly larger percentage of cases in group D had more severe POST than cases in group K (value, 0.05). But no statistically significant differences 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).

Baseline heart rate was recorded in both groups, Group K and Group D, before intubation. There wasn't a big difference in the two groups' mean heart rates after intubation, but group K had a much better distribution of mean heart rate after extubation than group D (P value < 0.05) in the cases that were looked at (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	

It was not significantly different between the two groups of patients in terms of their mean systolic and diastolic blood pressure before, during, and after intubation (P value > 0.05) (Figures 3 and 4).

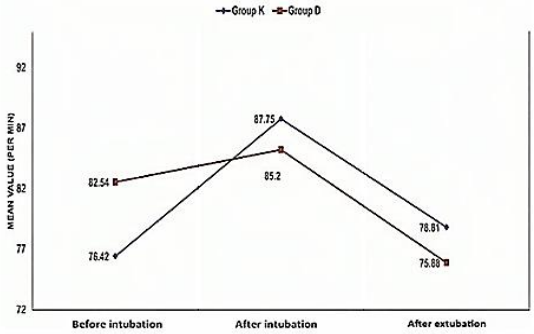

Figure 2- Inter-group distribution of mean heart rate.

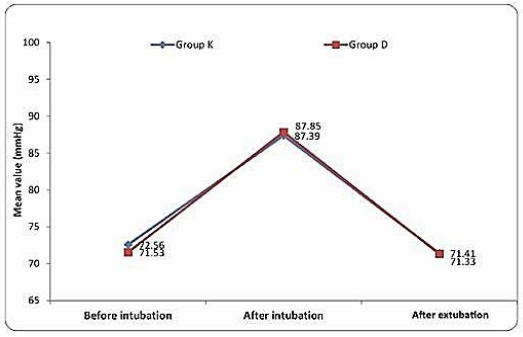

Figure 3- Inter-group Distribution of mean systolic BP.

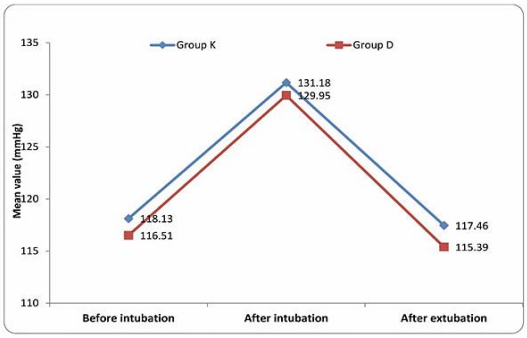

Figure 4- Inter-Group distribution of mean diastolic BP

Discussion

POST is considered one of the most common complications developing in patients undergoing surgery under general anesthesia 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 has been studied by

different researchers. The non-pharmacological methods studied to reduce incidence POST include ETT size, ETT cuff pressure, etc. It was observed that ETT of 6.0–7.5 mm internal diameter (ID) for females and 7.0–8.0 mm (ID) for male patients reduces POST significantly as compared to larger-sized 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 a 6.0 mm ID of ETT was used instead of a 7.0 mm ID. The decrease of 1 mm ID of ETT size remarkably decreases the incidence of POST [12].

It is very important to check the cuff pressure on a regular basis, since both too much and too little inflation of the tracheal tube cuff can lead to more problems.. The ideal range of ETT cuff pressure should be between 20-30 cm of H_2O. If the ETT cuff is too big, it puts too much pressure on the trachea, which can cause tracheal wall ischemia and necrosis. On the other hand, if the cuff is too small, it raises the risk of micro-aspiration, aspiration pneumonitis, pneumonia, and self-extubation [13]. Putting 2% lignocaine into the ETT cuff lowers the risk of and severity of POST because it acts as a local anesthetic and lowers inflammation in the trachea [14]. The various pharmacological agents studied to reduce the incidence of POST are corticosteroids, lidocaine, NSAIDs, and NMDA receptor antagonists. [5]. Different studies use gargling, intravenous, and nebulization to administer pharmacological drugs. Previous studies observed that the nebulization route, as opposed to the intravenous route, stabilized hemodynamic parameters during the intraoperative period [15]. Therefore, the nebulization route is considered safe and effective. Before and after intubation, Singla A et al. also said that the hemodynamic parameters are more stable when dexmedetomidine is nebulized instead of given intravenously [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. This indicates that patients who were nebulized with dexmedetomidine had a significantly higher incidence of POST compared to those who were 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., the 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 to our study.

ketamine and nebulized dexmedetomidine to see which would lower the risk of POST. They found that after 2 hours, the ketamine group had a lower risk of POST (14.58%) than the dexmedetomidine group (16.66%), which is the same as our study.

We also studied the inter-group comparison of grades of severity for 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 4-hour intervals. Similarly, the incidence of moderate POST in group K was 4.6%, and in group D it was 5.3% at 4 hours, respectively. However, we did not come across a severe grade of POST in group K, but 2.6% of patients in group D experienced severe POST at 4 hours (P value=0.031). Thus, at the 4-hour post-operative time interval, there was a 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. looked into how nebulized ketamine and dexmedetomidine affected POST and compared the changes in blood flow [18]. They have concluded that hemodynamic parameters, such as HR, SBP, and DBP, did not change significantly between the group of patients at any point in time, which is in line with our findings.

Limitations

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

We could not estimate the contribution of systemically absorbed drugs to the study findings because we have not measured the serum levels of the nebulized drugs. The pain relief might have been caused in part by other pain killers and anesthetics that were given before the surgery. However, they were given to both groups in the same amount, so they probably didn't change the difference between the results seen in the two groups. The use of polyurethane ETT instead of PVC cuffed tubes and their effect on POST have not been investigated as it was not a part of the study protocol.

Conclusion

Nebulization is a safe and effective route of administration with good patient acceptance Nebulization of both ketamine and dexmedetomidine before surgery is just as good at lowering the risk of and severity of POST with minimal effects on blood flow. However, at 4 hours, nebulized ketamine has shown a significant reduction in POST. Therefore, ketamine can be considered a better alternative to dexmedetomidine in reducing POST.

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