Original Article

Reduction in postoperative sore throat by preoperative nebulization with dexmedetomidine, ketamine or saline: A prospective, randomized-controlled trial

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Abstract

Background and Aims: Postoperative sore throat (POST) is a minor but distressing complication following general anesthesia. The current literature on the effect of preoperative nebulization with dexmedetomidine, or ketamine on POST is, however, sparse. So, we compared the effect of preoperative nebulization with these drugs on POST.

Material and Methods: One hundred and thirty-two American Society of Anaesthesiology (ASA) grade I-II patients undergoing elective laparoscopic surgeries under general anesthesia were randomized into three equal groups: D, K, or C to receive dexmedetomidine, ketamine, or saline as preoperative nebulization, respectively. The primary objective was to compare the incidence and severity of POST, as inferred from the patient interviews at 2, 6, 12, 24-h postoperatively.

Results: Group D had a significantly lower incidence (29.5%) and severity (12: mild; 1: moderate) of POST compared to group K (54.5% [21: mild; 3: moderate]) and group C (56.8% [19: mild; 6: moderate]), at 2-h postoperatively. The same trend was observed at 6-h postoperatively (group D: 22.7% [9: mild; 1: moderate]); group K: (40.9% [17: mild; 1: moderate]); group C (50% [17: mild; 5: moderate]). The mean arterial pressure was significantly lower in group D at 15 min intraoperatively (84.09 mmHg, $P = 0.018$) and immediate postoperatively (97.60 mmHg, $P = 0.034$). The postoperative sedation, nausea, and vomiting was not statistically significant.

Conclusion: Preoperative nebulization with dexmedetomidine is effective in the reduction of the incidence and severity of early POST.

Keywords: Dexmedetomidine, general anesthesia, ketamine, laparoscopic surgeries, postoperative sore throat (POST)

Introduction

Postoperative sore throat (POST) is a minor, however, unpleasant laryngeal sequel of endotracheal intubation. The incidence of POST varies from 14.4 to 50% and is common in females.[1] Many risk factors such as thyroid surgery, bucking on the tube, and nasogastric tube insertion contribute to POST.[1,2] It has a peak incidence at 2–6 h following extubation and an average duration of 16 ± 11 h.[3] It has been rated as the eighth most common postoperative adverse effect and contributes to morbidity, patient dissatisfaction, and compromises the quality of perioperative care.[4] The literature shows that ketamine gargle is effective in preventing POST.[5] However, it is less tolerable due to its bitter taste. Gargling has an uneven spread in the pharynx. It requires active participation and cooperation of the patient for effective drug

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Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.joacp_245_21

How to cite this article: Ittoop AL, Gupta P, Jain G, Tyagi N, Eda J, Shajahan S. Reduction in postoperative sore throat by preoperative nebulization with dexmedetomidine, ketamine or saline: A prospective, randomized-controlled trial. J Anaesthesiol Clin Pharmacol 2023;39:201-7.

Submitted: 19-May-2021 **Revised:** 14-Jun-2021
Accepted: 25-Jun-2021 **Published:** 25-Apr-2023

administration. It may be associated with aspiration or systemic toxicity due to the large volume of drug used. Nebulization of the drug has advantages such as the conversion of liquid preparation to droplets which get uniformly distributed over the pharynx, lower dose requirement for targeted effect, ease of administration, and above all, it is comfortable for the patient.

Though the effect of ketamine nebulization on POST has been studied,[6] the literature on the effect of dexmedetomidine nebulization is sparse. We hypothesized that preoperative nebulization with dexmedetomidine will reduce the incidence and severity of POST more effectively than nebulization with ketamine or saline. Hence, this study was designed to compare the effectiveness of preoperative nebulization with dexmedetomidine, ketamine, or placebo (normal saline) in reducing the incidence and severity of POST in patients undergoing endotracheal intubation for laparoscopic surgery under general anesthesia.

Material and Methods

This was a single-center, randomized, double-blinded, placebo-controlled study. The study protocol was approved by the institutional ethical committee (98/IEC/PGM/2019/ on 12/042019). Before enrolment of the patient, the study protocol was also registered at the clinical trials registry, India (CTRI/2019/06/019540). Written informed consent was obtained from all the participants. The American Society of Anaesthesiology physical status (ASA) I–II patients of 18–60 years of age, scheduled for laparoscopic surgery up to 2 h duration from August 2019 to October 2020 were recruited. Patients with anticipated difficult laryngoscopy, requiring more than one attempt for the insertion of an endotracheal or nasogastric tube, on steroids or nonsteroidal antiinflammatory drugs (NSAID) and having pre-existing laryngeal or pharyngeal disease (including sore throat), significant respiratory diseases, and known allergy for study drugs were excluded.

One hundred and thirty-two patients were randomly allocated to three groups using computer-generated random numbers and the group allocation was concealed via a sealed opaque envelope technique by an anesthesiologist blinded to the outcome variables. Group D received dexmedetomidine (Dextomid; Neon Laboratories) nebulization (1 μg/kg), group K received ketamine (Verket; Verve Health Care) nebulization (1 mg/kg), and group C received 0.9% saline nebulization (4 mL). Upon arrival to the preoperative area, the patients' vitals including non-invasive arterial blood pressure (NIBP), heart rate (HR), and peripheral oxygen saturation (SpO_2) were recorded and adequate venous access was established. The nursing staff opened the sealed envelope allocated to the patient and prepared the nebulization. All the study drug solutions were prepared in identical syringes with a final volume diluted to 4 mL by adding normal saline as required. Fifteen min prior to shifting to the operating room, another blinded nursing staff administered nebulization with compressor nebulizer delivering oxygen at a rate of 6 L/min for 15 min (till the drug volume gets exhausted).

The patient was then wheeled into the operating room and standard multipara monitoring (Drager Primus Infinity C 700) including HR, SpO_2, NIBP, electrocardiogram (ECG), Bispectral Index (BIS) (BIS Quatro; Covidien™), and Train of four stimulators (TOF) were attached. Intraoperative management was performed by a blinded anesthesiologist. The anesthesia was induced with fentanyl (2 μg/kg), propofol (2.5 mg/kg), and vecuronium (0.10 mg/kg). After induction, once the train of four monitoring showed zero twitches, laryngoscopy was performed by an experienced anesthesiologist (minimum 3 years of experience). The trachea was intubated with a 7.0 mm internal diameter cuffed polyvinyl endotracheal tube (PVC) in females and 8.0 mm in males. The patient was excluded if more than one attempt was required to intubate. The cuff was inflated by monitoring with the cuff pressure monitor. The cuff pressure was monitored throughout the surgery intermittently using a handheld Ambu® cuff pressure gauge to keep the pressure between 25 and 30 cm H_2O.

This was followed by painting, draping, and surgical incision. The anesthesia was maintained with oxygen, nitrous oxide, and sevoflurane to maintain the BIS between 45 and 55. Vecuronium was supplemented (0.02 mg/kg IV) if TOF ratio >30%. Fentanyl 0.5 μg/kg is given every h to supplement the intraoperative analgesia. Patients were continuously monitored for intraoperative hemodynamics throughout the surgery. At the end of the surgery, all the patients received Inj. Ondansetron 4 mg as prophylaxis for postoperative nausea and vomiting. The patients were reversed with neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg) and extubated in a deep plane. Following extubation, the patients were shifted to the post-anesthesia care unit. If excessive bucking/coughing occurred during the extubation, such incidences were noted.

The primary objective was to assess the incidence and severity of POST in the study groups. This was assessed by interviewing the patient at 2, 6, 12, 24 h in the post-anesthesia care unit by the blinded investigator. The sore throat was graded as 0: Nil; 1: Mild (complaints only on questioning); 2: Moderate (complaints on his/her own); 3: Severe (associated with hoarseness of voice).[6] The secondary objectives were to compare the perioperative hemodynamics, postoperative sedation, and postoperative nausea-vomiting among the study groups. The postoperative sedation was graded according to

the Modified Ramsay Sedation Scale.[7] Postoperative nausea and vomiting were assessed and graded by a 3-point ordinal scale.[8] Inj. Ondansetron 4 mg was used as a rescue treatment.

Statistics

To determine sufficient sample size, the power analysis was conducted through the G-Power statistical software. Taking an alpha error of 0.05, the power of 0.80, and an assumed effect size of 0.3 (medium effect size using Cohen's Convention and two tails), we required a sample size of 108. Considering a 20% dropout, we aimed to recruit 132 patients in the study (44 per group).[9] Data were coded and recorded in the MS Excel spreadsheet program. SPSS v23 [IBM Corp.] ® was used for data analysis. Descriptive statistics were elaborated in the form of mean, standard deviation, and median for the continuous variable. The categorical variables were presented as frequencies and percentages. Data were analyzed by an independent sample 't' test, Wilcoxon's test, Chi-square test, and Fischer's exact test. Statistical significance was kept at P value <0.05.

Results

A total of 150 patients were assessed for the study, of which 18 patients were excluded as they were not meeting the inclusion criteria. A total of 132 patients were included in this study, and they were randomly assigned to group D ($n = 44$), group K ($n = 44$), or group C ($n = 44$). All the randomized patients were analyzed at the end of the study [Figure 1 represents the consort flow diagram].

The three groups were comparable with respect to the demographic data including age, gender distribution, height, weight, body mass index (BMI), ASA status, and modified Mallampati grade. The three groups were also comparable with respect to the intubation attempt, Cormack Lehane (CL) grade, presence or absence of Ryle's tube, the total fentanyl used intraoperatively, the endotracheal tube cuff pressure, and the duration of anesthesia [Table 1]. No patient had excessive bucking on the tube during extubation.

At 2-, 6-, 12-, and 24-h postoperative time point, the overall incidence of POST was 47, 37.9, 14.4, and 4.4%, respectively. Postoperatively at the end of 2 h, 25 (19: mild; 6: moderate) patients in the saline (control) group, 24 (21: mild; 3: moderate) in the ketamine group, and 13 (12: mild; 1: moderate) in the dexmedetomidine group had POST ($P = 0.018$) [Tables 2 and 3]. At 6 h postoperatively, 22 (17: mild; 5: moderate) patients in the saline (control) group, 18 (17: mild; 1: moderate)

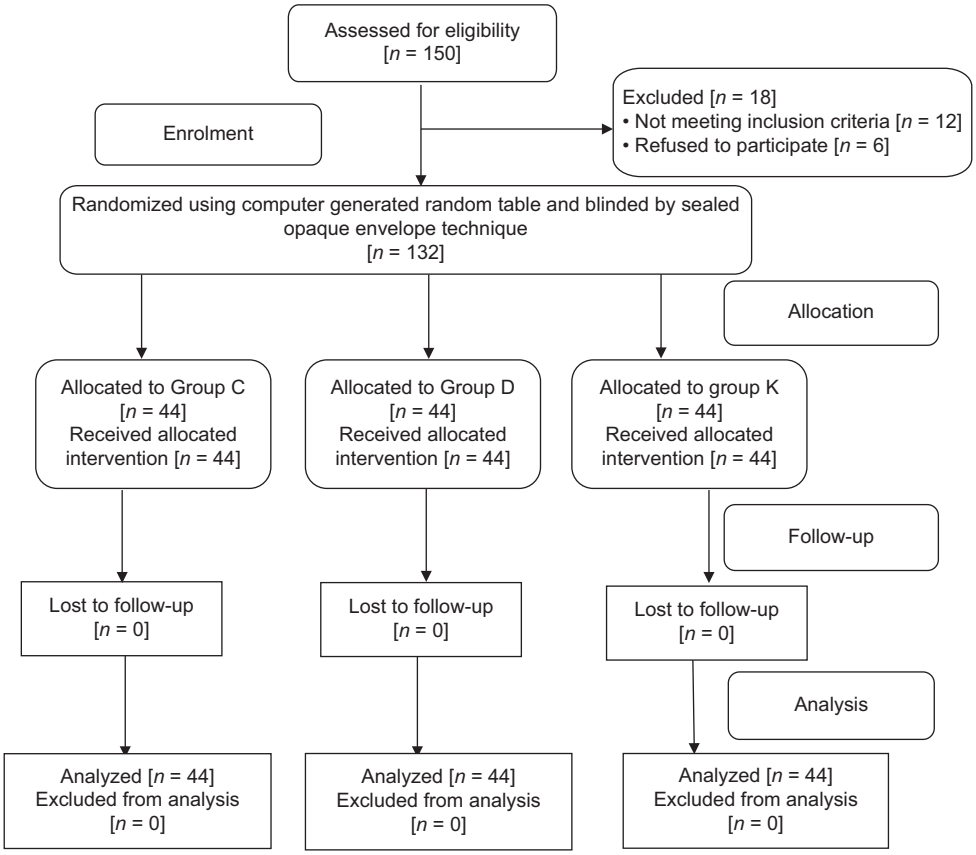

Figure 1: CONSORT Flow diagram

Table 1: Association between group and parameters

Parameters	Group			*P*
	C [*n*=44]	K [*n*=44]	D [*n*=44]	
Age [Years]	43.27±10.36	44.00±11.21	40.25±10.46	0.182
Age				0.264
20-29 Years	8 [18.2%]	4 [9.1%]	10 [22.7%]	
30-39 Years	7 [15.9%]	12 [27.3%]	11 [25.0%]	
40-49 Years	13 [29.5%]	9 [20.5%]	13 [29.5%]	
50-59 Years	16 [36.4%]	19 [43.2%]	10 [22.7%]	
Gender				0.229
Male	7 [15.9%]	11 [25.0%]	5 [11.4%]	
Female	37 [84.1%]	33 [75.0%]	39 [88.6%]	
Height [cm]	159.70±7.07	159.48±6.91	158.86±5.71	0.826
Weight [kg]	61.07±10.41	61.98±10.03	60.80±7.03	0.623
BMI [kg/m^2]	23.82±2.83	24.26±2.72	24.09±2.54	0.593
ASA				0.560
Grade 1	39 [88.6%]	36 [81.8%]	39 [88.6%]	
Grade 2	5 [11.4%]	8 [18.2%]	5 [11.4%]	
Intubation Attempt [First]	44 [100.0%]	44 [100.0%]	44 [100.0%]	1.000
CL Grade [Grade 1]	44 [100.0%]	44 [100.0%]	44 [100.0%]	1.000
Ryle's Tube [Inserted]	44 [100.0%]	44 [100.0%]	44 [100.0%]	1.000
Duration Of anesthesia [Min]	59.55±11.45	61.70±12.39	60.68±13.54	0.623
Cuff Pressure [mmHg]	25.55±0.66	25.55±0.63	25.30±0.46	0.089
Total Fentanyl Used Intraoperatively [mg]	103.41±12.75	101.14±7.54	101.14±7.54	0.438

**BMI-Body mass index; †CL Grade- Cormack Lehane grading*

Table 2: Association between group and incidence of POST

POST	Group				*P*
	C	K	D	Total	
2 h Postoperative	25 [56.8%]	24 [54.5%]	13 [29.5%]	62 [47.0%]	0.018
6 h Postoperative	22 [50.0%]	18 [40.9%]	10 [22.7%]	50 [37.9%]	0.027
12 h Postoperative	8 [18.2%]	6 [13.6%]	5 [11.4%]	19 [14.4%]	0.650
24 h Postoperative	3 [6.8%]	2 [4.5%]	1 [2.3%]	6 [4.5%]	0.871

**POST - Post- operative sore throat*

Table 3: Association between group and POST severity

POST Severity	Group				*P*
	C	K	D	Total	
2 h Post -Operative					
Mild	19 [43.2%]	21 [47.7%]	12 [27.3%]	52 [39.4%]	0.039
Moderate	6 [13.6%]	3 [6.8%]	1 [2.3%]	10 [7.6%]	
6 h Postoperative					
Mild	17 [38.6%]	17 [38.6%]	9 [20.5%]	43 [32.6%]	0.037
Moderate	5 [11.4%]	1 [2.3%]	1 [2.3%]	7 [5.3%]	
12 h Postoperative					
Mild	7 [15.9%]	6 [13.6%]	5 [11.4%]	18 [13.6%]	0.775
Moderate	1 [2.3%]	0 [0.0%]	0 [0.0%]	1 [0.8%]	
24 h Postoperative					
Mild	3 [6.8%]	2 [4.5%]	1 [2.3%]	6 [4.5%]	0.871

**POST- Post- operative sore throat*

patients in the ketamine group, and 10 (9: mild; 1: moderate) patients in the dexmedetomidine group had POST (P = 0.027) [Tables 2, 3 and Figures 2, 3]. At 12 h postoperatively, 8 (7: mild; 1: moderate) patients in the saline (control) group, 6 (6: mild; 0: moderate) patients in the ketamine group, and 5 (5: mild; 0: moderate) patients in the dexmedetomidine group had POST (P = 0.654) [Tables 2 and 3]. At 24 h postoperatively, 3 (3: mild) patients in the saline (control) group, 2 (2: mild) patients in the ketamine group and

1 (1: mild) patient in the dexmedetomidine group had POST ($P = 0.871$) [Tables 2, 3 and Figures 2, 3].

Hemodynamic parameters like HR systolic BP, diastolic BP, and mean arterial pressure (MAP) were recorded at preoperative, pre-nebulization, post-laryngoscopy, intraoperatively at 15 mini interval, immediate postoperative, 2-h postoperative, 6-h postoperative, 12-h postoperative, and 24-h postoperative time point. MAP and HR did not show any significant change among the groups at any time point [Figures 4 and 5].

Discussion

In our study, the incidence and severity of POST were significantly lower in the dexmedetomidine group at 2- and 6-h postoperative time point. However, the reduction in the incidence and severity of POST was not statistically significant at 12- and 24-h postoperative time points. The incidence and severity of POST were comparable among the ketamine and saline group at all the observed time points.

Compared to the previous literature, the incidence of sore throat was higher in our study even though smooth intubation was done by an experienced anesthesiologist and optimal cuff pressure was maintained.[1] This may be due to the higher preponderance of females in all three groups and the insertion of the Ryle's tube in all the patients.[1,2]

Dexmedetomidine, a super-selective alpha 2 agonist, reduces the transmission of nociceptive signals at the dorsal horn of the spinal cord. The mechanism of action of topically applied dexmedetomidine and topical analgesic preparations of the drug is still under research. Recently, Thomas *et al.*,[10] used dexmedetomidine (50 mcg in 4 ml normal saline (NS)) as preoperative nebulization and it was equally efficacious as ketamine (50 mg in 4 mL NS) nebulization in reducing the incidence and severity of POST at 0, 2, 6, 12, 24 h postoperative time point. However, in this study, the dose of nebulization was not calculated according to the body weight and the endotracheal tube cuff pressure was not monitored. The evaluation of POST in their study was done by the nursing staff in the post anesthesia care unit (PACU) leading to observer bias.

Nebulizations would act more locally at the desired site, and also are, likely to have a much lower concentration in the blood, hence containing the possible systemic adversities. Cardiorespiratory depression following intravenous dexmedetomidine is supported by a study conducted by Kim *et al.*,[11] which evaluated the efficacy of intravenous

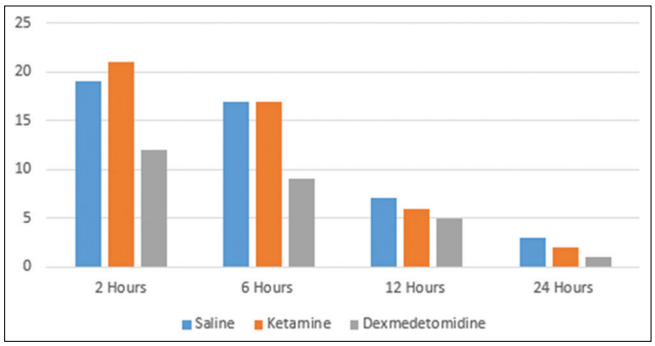

Figure 2: Incidences of mild postoperative sore throat (POST) among the three groups

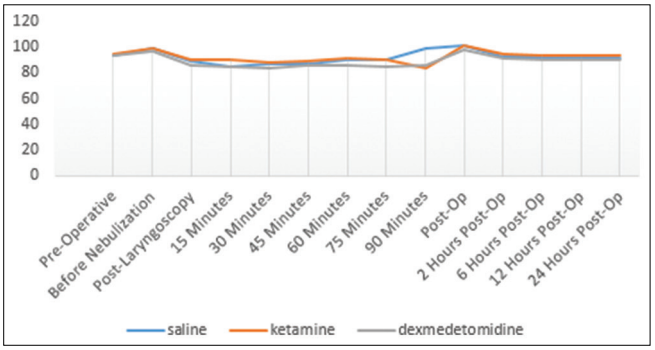

Figure 4: Variation in the mean arterial pressure (mmHg) during the perioperative period

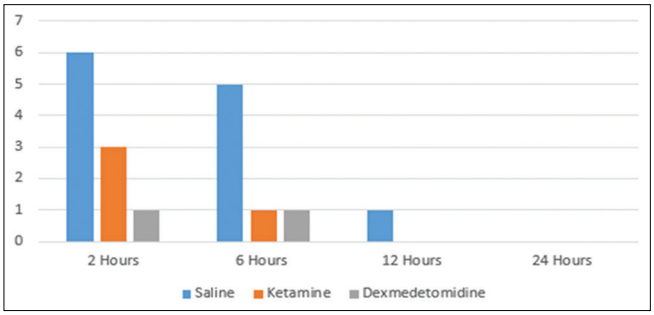

Figure 3: Incidences of moderate postoperative sore throat (POST) among the three groups

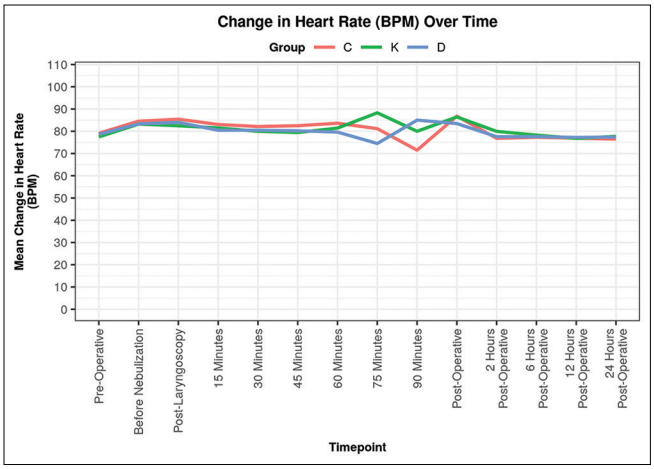

Figure 5: Variation in the heart rate during the perioperative period

dexmedetomidine and compared it with remifentanil infusion. The sore throat was better controlled with dexmedetomidine, however, the use of an intravenous route for both the drugs brought about systemic effects of cardiorespiratory depression.

Ketamine is an N-methyl D-Aspartate (NMDA) receptor antagonist that acts peripherally on the sensory afferent nerve endings and also has anti-inflammatory effects. In our study, the ketamine group had a significantly higher incidence and severity of POST as compared to the dexmedetomidine group, though it was lower than saline at all observed time points, although non-significant statistically. In a study by Franco-Cabrera *et al.*,[12] on the effect of ketamine nebulization on POST, they concluded that ketamine nebulization does not cause a statistically different reduction in POST. Similar results were observed by Rajkumar *et al.*,[13] when they studied the effect of ketamine gargle and saline on the reduction of POST. In this study, the difference between ketamine, and saline groups was minimal with respect to mild and early POST, however, it was higher with respect to moderate POST, although not statistically significant. The minimal difference between saline and ketamine in early and mild POST due to the hydrating and soothing effect of saline helping the inflamed throat.

Isotonic saline nebulization has also been found useful as a hydration treatment for throat dryness and irritation. Tanner *et al.*,[14] in a study, analyzed the effect of nebulized water and nebulized saline on throat dryness after the laryngeal desiccation challenge in the Sjögren's syndrome patients. Nebulized saline had a greater effect than nebulized water in relieving throat dryness. This hydrating effect of nebulized saline may help in soothing the inflamed throat after airway manipulation.

The hemodynamic variations with each of them were also studied, in a pursuit to find an agent which leads to an appropriate mitigation of POST with minimal risk of hemodynamic instability. No significant variations were noted during any time in the heart rates. A similar result was observed by Kumar NRR *et al.*,[15] in their study to find out the efficacy of nebulized dexmedetomidine in blunting the hemodynamic response to intubation. Qin *et al.*[16] had studied and compared the efficacy of dexmedetomidine as a nasal spray at 1 mcg/kg and 1.5 mcg/kg on preoperative sedation, perioperative hemodynamics, and incidence of postoperative adverse reactions. This study showed similar efficacy in preventing postoperative adverse events in both groups, but the MAP was seen to drop with a higher dose. We opted for the lower dose of 1 mcg/kg based on this observation. In our study, the variation of MAP among the groups was not significant. Stable hemodynamic parameters are desirable for better intraoperative and postoperative management.

The difference in the sedation scores among the groups was not statistically significant. This may be due to the lower systemic absorption of the nebulized drug. The incidence of post operative nausea and vomiting (PONV) was also comparable among the groups.

This study showed that dexmedetomidine had a much superior result in decreasing early POST which is the eighth-most reported complication leading to patient dissatisfaction.

Our study had certain limitations. We did not measure the blood concentrations of the study drugs due to resource and financial constraints. This would have helped to understand the pharmacokinetics of the nebulized drug and the mechanism of reduction of POST. POST was not assessed beyond the 24-h postoperative time point as the patients were discharged. This would have helped in calculating the mean duration of POST and detect any late-onset POST.

In conclusion, preoperative dexmedetomidine nebulization can be used effectively in patients undergoing surgery under general anesthesia requiring endotracheal intubation and is superior to preoperative nebulization with ketamine for reducing the incidence and severity of early POST.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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