

Dexmedetomidine nebulisation attenuates post-operative sore throat in patients undergoing thyroidectomy: A randomised, double-blind, comparative study with nebulised ketamine

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ABSTRACT

Background and Aims: Endotracheal intubation is the predominant cause of airway mucosal injury, resulting in post-operative sore throat (POST), with an incidence of 20-74%, which brings immense anguish to patients. This study was conducted to evaluate and compare the efficacy of nebulised dexmedetomidine and ketamine in decreasing POST in patients undergoing thyroidectomy. **Methods:** Patients were randomly allocated into two groups of 50 each; Group 1 received ketamine 50mg (1mL) with 4mL saline nebulisation, while Group 2 received dexmedetomidine 50µg (1mL) with 4mL saline nebulisation for 15 min. GA was administered 15 min after completing nebulisation. POST monitoring was done at 0,2,4,6,12 and 24h after extubation. POST was graded on a four-point scale (0-3). The statistical analysis were performed using Statistical Package for Social Sciences (SPSS) software version 17.0. Fisher Exact-t-test, Chi square test, Student *t*-test, Paired *t* test and repeated measure analysis of variance (ANOVA) were used for analysis. **Results:** The overall incidence of POST in this study was 17%: POST was experienced by seven patients (14.3%) in ketamine and 10 patients (20.4%) in dexmedetomidine group ($P = 0.424$). There was no statistically significant difference in the incidence of POST between the two groups at 0,2,4,6,12 and 24h post-operatively. Severity of sore throat was also significantly lower in both groups at all time points. A statistically significant increase in heart rate, systolic and diastolic blood pressure was noted in ketamine group, post nebulisation. **Conclusion:** Pre-operative dexmedetomidine nebulisation can be utilised as a safe and ideal alternative to ketamine nebulisation in attenuating POST, with less haemodynamic derangement.

Key words: Dexmedetomidine, general anaesthesia, ketamine, nebulisation, sore throat, thyroidectomy

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INTRODUCTION

Post-operative sore throat (POST) is a feeling of discomfort usually voiced by the patients during the post-operative recovery period, following surgeries under general anaesthesia (GA). Even though POST is of a lesser concern to the treating physician, it causes significant agony and anguish to the patient, besides bringing immense displeasure with the quality of recovery after anaesthesia.^[1]

The reported incidence of POST following GA varies between 20-74%.^[2,3] On comparing with other surgeries, the occurrence of POST is shown to be

higher in post thyroidectomy patients.^[4,5] Numerous trials had been conducted in the past using different pharmacological and non-pharmacological methods for attenuating POST with varying outcomes.^[6-9]

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Nowadays, nebulisations are better accepted and tolerated by the patients than gargle, as it spares them from the bitter taste of the drug. The chance of aspiration is also less likely as only a reduced volume is administered when compared to the volume needed for gargle. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist, which has already been in use in the nebulised form, for attenuating POST, due to its anti-nociceptive and anti-inflammatory properties.^[10,11] Dexmedetomidine is a colorless, tasteless and odorless drug with a selective α -2 adrenergic agonistic action, which causes sedation and analgesia.^[12] No study has been conducted so far to evaluate the effectiveness of nebulised dexmedetomidine in decreasing POST. Nevertheless dexmedetomidine has already been in use in a nebulised form, and being a highly lipid soluble agent it has good systemic absorption on transmucosal administration.

Hence, we planned this study to evaluate and compare the effectiveness of nebulised dexmedetomidine and nebulised ketamine in alleviating POST in patients undergoing thyroidectomy under GA.

METHODS

After procuring the approval of the Institutional Ethics Committee (approval number: 07/IEC/19/AIMS-C; dated: 22-6-2019) and informed written consent, 100 patients, in the age group of 18-60 years, with American Society of Anaesthesiologists (ASA) physical status (PS) 1-2, who were scheduled to undergo elective thyroid surgery under general anaesthesia (GA) with endotracheal intubation were recruited in this prospective, double-blind, randomised comparative trial (CTRI/2019/07/020082). Exclusion criteria included patients with a history of pre-operative sore throat, upper respiratory tract infection, known allergy to study drug, pregnancy, chronic obstructive pulmonary disease and Mallampati grade >2. The enlisted patients, who needed more than one intubation attempt or developed any intra-operative or post-operative complication were also excluded from further evaluation and analysis.

The patients drafted for the study remained fasted for 6 hours prior to surgery. Anaesthesia protocol was standardised for all patients. Patients were randomly allocated into two groups with the help of a computer-formulated randomisation technique, using consecutively numbered opaque sealed envelopes, which were arranged by an anaesthesiologist who

did not take part in the study. After opening those envelopes, the nebulisation solution was made ready by an anaesthesia assistant according to the assigned group. The anaesthesia assistant who prepared the solution did not take part in the subsequent analysis of these patients. Patients were also blinded as both the study preparations were colorless and tasteless.

The enrolled study participants were randomised into two groups of 50 each:

Group 1 received ketamine 50mg (1mL) with saline (4mL) nebulisation

Group 2 received dexmedetomidine 50 μ g (1mL) with saline (4mL) nebulisation,

The drug was delivered using a nebulisation mask for 15 min, with the help of a wall-attached oxygen driven source (8L, 50psi). Fifteen minutes after finishing nebulisation, GA was induced with intravenous (IV) fentanyl 2 μ g/kg and IV propofol 2 mg/kg. In order to guarantee minimal trauma, three minutes after giving vecuronium bromide 0.1 mg/kg IV, a swift and a gentle laryngoscopy was performed by a well experienced anaesthesiologist, which lasted less than 15 sec, using a Macintosh blade (size 3 or 4). A sterile single lumen cuffed polyvinyl chloride (PVC) endotracheal tube with an inner diameter of 7-7.5mm in females and 8-8.5mm in males was used for tracheal intubation. Later, the cuff of the endotracheal tube was inflated with room air, till no audible air leakage was detected.

Anaesthesia was maintained using 33% oxygen in nitrous oxide and sevoflurane (1-1.2 MAC). For pain relief, paracetamol 1g IV was administered during surgery, followed by 6th hourly in the post-operative period. Ondansetron 4mg IV was given 30 min preceding the end of surgery and thereafter every eight hours post-operatively. Once the surgery was completed, the oropharynx was gently suctioned using a soft suction catheter and reversal of the neuromuscular blockade was done with neostigmine 50 μ g/kg IV and glycopyrrolate 10 μ g/kg IV. After regaining complete consciousness, the patient was extubated.

In the post anaesthesia care unit (PACU), sore throat was evaluated by the nursing staff in PACU, who was oblivious of the allocated group of the patient at 0,2,4,6,12 and 24h after extubation, during the post-operative period. Grading of POST

was done using a four-point scale (0-3)^[13]: 0 for no sore throat; 1 for mild sore throat (complains of sore throat only when asked); 2 for moderate sore throat (complains of sore throat even without asking); and 3 for severe sore throat (with change of voice or hoarseness, also may be associated with throat pain). Even after 24 hours, if patients still complained of moderate or severe POST, lukewarm saline gargle as well as decongestants would be prescribed for them. If the symptoms still persisted, an oto-rhino-laryngology consultation would be ensured. Haemodynamic variables such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MABP) were also recorded at pre-nebulisation, pre-induction, 0,2,4,6,12 and 24 h after extubation. Any other side effects if present, were also recorded 8th hourly for 24 hours post-operatively.

The primary aim of our study was to examine the effectiveness of dexmedetomidine nebulisation in attenuating POST in adult patients undergoing thyroidectomy under GA, when compared to ketamine nebulization and also to assess the incidence and severity of POST among the two groups. The secondary aims involved the monitoring of side-effects such as cough, dry mouth, post-operative nausea and vomiting (PONV), hallucinations, respiratory depression and haemodynamic instability in both the groups.

Sample size was formulated from the study,^[10] with incidence of POST in Group Saline as 46% and Group Ketamine as 20%. With the power of study at 80% and 95% confidence level, the minimum sample size needed was estimated to be 48 in each group. Considering possible loss during follow-up, we had taken a sample size of 50 in each group.

The statistical calculations were performed using the software Statistical Package for the Social Sciences for Windows version 17.0 [SPSS Inc., Chicago, IL, USA]. The following statistical methods were applied in the present study. Differences in the age, weight and duration of surgery among the groups were done using Student *t*-test. ASA grading and differences in the incidence of POST were analysed using Fisher's exact test or Chi-Square test. Continuous data was represented as mean and standard deviation. Paired *t*-test and repeated measure analysis of variance (ANOVA) were also used for analysis. Paired *t*-test was

used to compare the pre-nebulisation and pre-induction haemodynamic variables. Level of significance was set at 0.05 and all tests were two-sided.

RESULTS

From the 117 patients we screened for the study, 17 patients were excluded. Hence, a total of 100 patients were recruited and assigned into two groups of 50 each. Among them, one patient from ketamine group developed post-extubation laryngospasm and one patient in the dexmedetomidine group had stridor in the post-operative period. Both these patients discontinued the study, while rest of the 98 patients completed the study and were subsequently followed up and analysed [Figure 1]. A comparable distribution of age, gender, body weight, ASA PS and duration of surgery was noted among the two groups [Table 1].

The overall incidence of POST was 17% in our study: POST was experienced by seven patients (14.3%) in ketamine and 10 patients (20.4%) in dexmedetomidine group ($P = 0.424$). Between the two groups, no statistically significant difference was noticed in the incidence of POST at 0,2,4,6,12 and 24h post-operatively [Table 2].

Severity of sore throat was also significantly lesser in both groups at all time intervals [Table 3]. Only two patients in dexmedetomidine group and one patient in ketamine group had moderately severe sore throat. None of the patients in both groups developed severe sore throat.

While considering haemodynamic parameters, a statistically significant rise in HR, SBP and DBP ($P = 0.002$, $P = 0.035$ and $P = 0.001$ respectively) was noted in ketamine group, when pre-nebulisation and pre-induction values were compared [Table 4]. Adverse effects such as PONV, dry mouth, cough, hoarseness, hallucinations or respiratory depression were absent during the entire period of observation.

Table 1: Patient Characteristics

Characteristics	Group 1 (Ketamine)	Group 2 (Dexmedetomidine)	<i>P</i>
Age (years)	45.08 (10.11)	45.53 (10.002)	0.801
Weight (kg)	66.86 (15.75)	64.10 (6.97)	0.830
Duration of surgery (min)	100.51 (31.24)	106.22 (45.01)	0.365
Male/female	9/40	10/39	0.798
ASA PS (grade 1/2)	16/33	15/34	0.828

Data expressed as Mean (standard deviation) or Number. ASA PS: American Society of Anaesthesiologists physical status. *Significant at the 0.05 level

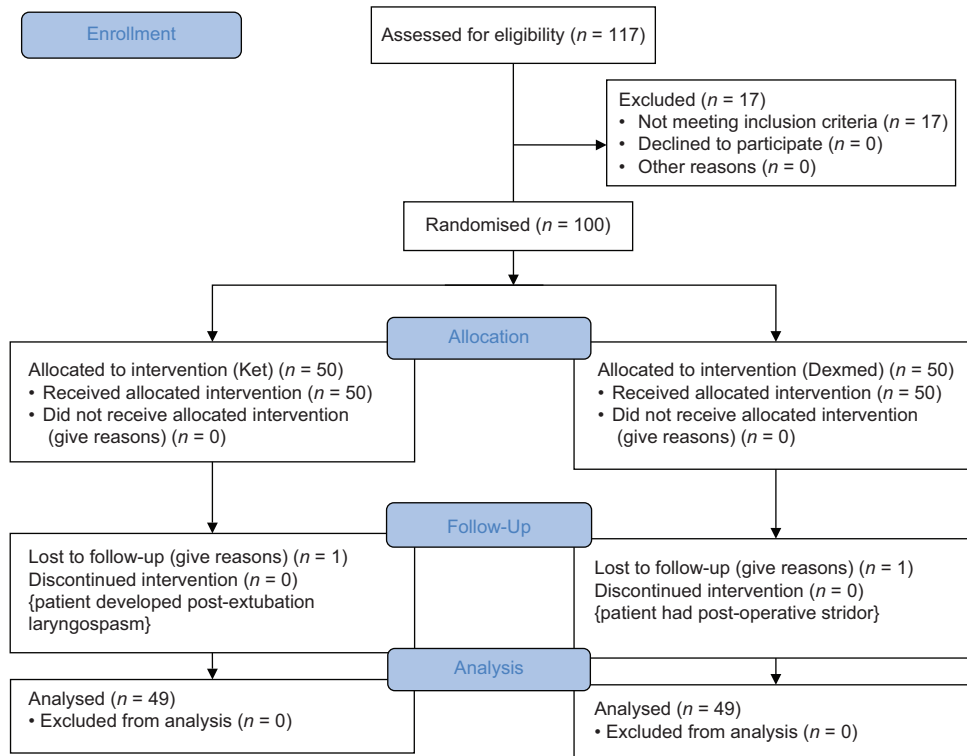


Figure 1: CONSORT Flow Diagram

Time	POST	Group 1 (Ketamine)	Group 2 (Dexmedetomidine)	P
0 h	Absent	46	44	0.461
	Present	3	5	
2 h	Absent	42	39	0.424
	Present	7	10	
4 h	Absent	43	44	0.724
	Present	6	5	
6 h	Absent	44	44	1.0000
	Present	5	5	
12 h	Absent	45	44	0.727
	Present	4	5	
24 h	Absent	45	44	0.727
	Present	4	5	

*Significant at the 0.05 level. POST: Post-Operative Sore throat

DISCUSSION

In our study, there was no statistically significant difference in the incidence of POST between the two groups at 0, 2, 4, 6, 12 and 24h post-operatively. A significant reduction in the severity of sore throat was noticed in both groups at all time points during the first post-operative day. Moderately severe sore throat was noted only in two patients in dexmedetomidine group and in one patient in ketamine group. No patients in both groups developed severe sore throat.

Post-operative sore throat occurs probably as a consequence of injury to the mucosa of pharynx during laryngoscopy or as an injury to tracheal tissues either during intubation or extubation, which may trigger an aseptic inflammatory reaction in the tracheal mucosa.^[14,15] Chan *et al.*^[16] in his study using ketamine gargle, came to a conclusion that the topical action of ketamine reduced the incidence of POST more than the systemic effect. Also, Ahuja *et al.*^[10] and Thomas *et al.*^[11] proposed that pre-operative administration of nebulised ketamine significantly declined the incidence and severity of sore throat in the post-operative period. Hence, the topical influence of ketamine nebulisation, which abated the local inflammation and also triggered a peripheral analgesic effect, with its NMDA-antagonistic and anti-inflammatory actions can be the reason for the significant attenuation of POST in our ketamine group.^[10,11,13,17]

Many multi-faceted protective functions of dexmedetomidine which even include the inhibitory action on pro-inflammatory cytokine production, have been disclosed by several pre-clinical studies on murine models.^[18-20] Zhang and Zhang^[21] in their study concluded that dexmedetomidine decreased inflammatory responses, thereby reducing the chances of cerebral injury following cardio pulmonary bypass

Table 3: Severity of Post-operative sore throat in patients

Time	Grades	Group 1 (Ketamine)	Group 2 (Dexmedetomidine)	P
0 h	0	46	44	0.749
	1	2	3	
	2	1	2	
2 h	0	42	39	0.337
	1	7	8	
	2	0	2	
4 h	0	43	44	0.494
	1	6	4	
	2	0	1	
6 h	0	44	44	1.0000
	1	5	5	
12 h	0	45	44	0.727
	1	4	5	
24 h	0	45	44	0.727
	1	4	5	

*Significant at the 0.05 level

Table 4: Comparison of haemodynamic parameters during pre-nebulisation and pre-induction

	Pre Nebulisation	Pre Induction	P
Heart Rate (beats/min)			
Group 1 (Ketamine)	78.90±14.81	83.39±11.003	0.002 *
Group 2 (Dexmedetomidine)	80.49±11.25	77.76±12.88	0.072
SBP (mm Hg)			
Group 1	119.37±14.48	125.37±19.21	0.035 *
Group 2	138.69±18.98	134.02±34.52	0.299
MABP (mmHg)			
Group 1	90.06±10.094	92.86±13.416	0.154
Group 2	103.53±12.17	99.69±19.116	0.153
DBP (mmHg)			
Group 1	75.29±8.32	80.59±9.49	0.001 *
Group 2	83.24±11.099	83.18±13.97	0.980

*Significant at the 0.05 level. SBP: Systolic Blood Pressure, MABP: Mean Arterial Blood Pressure, DBP: Diastolic Blood Pressure

in patients undergoing cardiac valve replacement. They established a significant reduction in the serum concentrations of inflammatory mediators such as TNF- α , IL-6 and S100 β in their study. Similar results with dexmedetomidine were also obtained by Zhu^[22] in his study in patients with one lung ventilation. Also, Li *et al.*^[23] conducted a meta-analysis to scrutinise the available data on the effectiveness of dexmedetomidine on inflammatory modulators, when used peri-operatively. They concluded that when administered along with GA, dexmedetomidine produced remarkable reduction in the levels of serum IL-6, IL-8 and TNF- α post-operatively. In view of these anti-inflammatory effects shown by dexmedetomidine, many authors are now advocating its pre-emptive administration for better results.^[24,25] Iirola *et al.*^[12] in their study evaluating the pharmacokinetic and pharmacodynamic properties of intranasal

dexmedetomidine observed a rapid and efficient absorption of dexmedetomidine when administered intranasally. Therefore, the significant decline in the incidence and severity of POST that we noted in our dexmedetomidine group can be attributed to the significant reduction in the inflammatory mediators caused by nebulised dexmedetomidine when administered pre-operatively, along with its analgesic action.

Following nebulisation, a marked increase in the pre induction values of haemodynamic parameters such as HR, SBP and DBP was recorded in the ketamine group in our study, which may be because of the systemic absorption of ketamine. Similar results were also obtained by Segaran *et al.*^[26] in the ketamine group in their study, while comparing and evaluating the efficacy of nebulised magnesium sulphate with nebulised ketamine in diminishing POST. The studies done by Ahuja *et al.*^[10] and Thomas *et al.*^[11] showed no such haemodynamic variations.

The overall incidence of POST after GA, was reported to be between 20-74%,^[2,3] whereas following total thyroidectomy, the incidence of POST was as high as 80%. Kadri *et al.*^[4] in his study postulated that POST was even dependent on the types of thyroid surgery and he noticed that 59.6% of patients had POST following partial thyroidectomy, 87.7% following subtotal thyroidectomy and 100% following total thyroidectomy. Jung *et al.*^[5] also had similar findings, where he recorded an incidence of POST of 83.9% in patients after total thyroidectomy. In our study majority of the patients underwent total thyroidectomy, only 11 patients had hemi, near total or subtotal thyroidectomy. Because of the minimal number of patients who had surgeries other than total thyroidectomy in our study, we were not able to compare POST with the different types of thyroid surgeries. However, even with the majority of patients undergoing total thyroidectomy, our study showed an overall incidence of POST of only 17%, with only 20% in dexmedetomidine group. The incidence of POST in ketamine group (14.3%) was much lower in comparison to the study done by Ahuja *et al.*^[10] (20%), while it was comparable to the study done by Thomas *et al.*^[11] (14.6%), where both these studies evaluated the effectiveness of nebulised ketamine in reducing POST.

From many previous studies, numerous factors have been recognised as those leading to POST, including patient age, gender, cuff design variations, intra cuff pressure as well as endotracheal tube size.^[8,9,27] But,

our study showed a comparable distribution of age, gender, body weight, ASA PS and duration of surgery among both groups.

There are a few limitations to our study. Monitoring of cuff pressure was not done during GA and no sedation scale was used during the study. The dose we used for both drugs was a fixed dose. We were also unable to measure the serum levels of the studied drugs and follow-up analysis was not done beyond 24 h.

CONCLUSION

Pre-operatively administered dexmedetomidine nebulisation is as effective as ketamine nebulisation in attenuating POST, with less haemodynamic derangement. Hence, nebulised dexmedetomidine may be considered as a safe alternative to nebulised ketamine for decreasing POST.

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Conflicts of interest

There are no conflicts of interest.

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