Title: The effect of preoperative dexmedetomidine nebulization on the hemodynamic response to laryngoscopy and intubation: A randomized control trial

Running title: Nebulized dexmedetomidine and laryngoscopy response

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Disclosures, Conflicts of Interest and Funding: None

Abstract word count: 250; Manuscript word count: 2776

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**Trial registration:** Clinical Trials Registry of India (CTRI) (trial registration number: CTRI/2019/01/017060; trial registration date: 14/01/2019; Principal Investigator: Dr. Satyajeet Misra)

**Author Contributions**

1. Satyajeet Misra - This author generated the study hypothesis, patient recruitment, data acquisition and drafting the initial and final versions. Approved the final version and is responsible for the study conducted.

2. Bikram K Behera - This author helped in generation of study hypothesis, patient recruitment, statistical analysis and revising the final manuscript for intellectual content. Approved the final version and is responsible for the study conducted.

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The effect of preoperative dexmedetomidine nebulization on the hemodynamic response to laryngoscopy and intubation: A randomized control trial

**Running title:** Nebulized dexmedetomidine laryngoscopy
Abstract

**Background:** Dexmedetomidine, an alpha-2 agonist, has been used for attenuation of hemodynamic response to laryngoscopy, but not through the nebulized route. The aims of this study were to evaluate the effect of preoperative dexmedetomidine nebulization on the hemodynamic response to laryngoscopy-intubation, intraoperative anesthetic-analgesic requirements and recovery outcomes.

**Methods:** 120 ASA I & II adult patients, of either gender, undergoing elective surgeries requiring tracheal intubation were enrolled and randomized to receive nebulized dexmedetomidine (1 µg/kg in 3–4 ml of 0.9% saline) or 0.9% saline (3–4 ml), 30 minutes before anesthesia induction. Heart rate and non-invasive systolic blood pressures were studied for 10 minutes following laryngoscopy.

**Results:** After laryngoscopy, linear mixed effect modelling showed significantly lower trend of increase in heart rate in the dexmedetomidine group versus saline (P = 0.01). However, there was no difference in the systolic blood pressure changes between the two groups (P = 0.90). Induction dose of propofol (P < 0.001), intraoperative fentanyl consumption (P = 0.007) and isoflurane requirements (P = 0.01) were significantly lower in the dexmedetomidine group. There was no difference in the 2-hr postoperative nausea and vomiting (PONV) (P = 0.61) or sore-throat (P = 0.74).

**Conclusions:** Nebulized dexmedetomidine 1 µg/kg attenuated the increase in heart rate but not systolic blood pressures following laryngoscopy; and reduced the intraoperative anesthetic and analgesic consumption. There was no effect on early PONV, sore-throat or increase in incidence of adverse effects. Nebulized dexmedetomidine may represent a favorable alternative to the intravenous route in short duration surgeries.

**Keywords:** Dexmedetomidine; Hemodynamic response; Intubation; Laryngoscopy; Nebulization.
Introduction

Direct laryngoscopy and tracheal intubation following induction of anesthesia are associated with hemodynamic changes due to increased sympathoadrenal activity which may result in hypertension and/or tachycardia [1,2]. Although transient, this exaggerated response may precipitate hypertensive crises, myocardial ischemia, arrhythmias or increases in intracranial pressure in susceptible individuals [1]. Various drugs including local anesthetics, beta-blockers, calcium channel blockers, narcotic analgesics have been tried to blunt the laryngoscopy and intubation response with varied success [3–9].

Dexmedetomidine is a potent and highly selective alpha-2 receptor agonist with sympatholytic, sedative, amnestic and analgesic properties [10]. Its pleiotropic effects have led to its increasing use in the perioperative period [10]. Dexmedetomidine has been studied through intravenous [11–15], intranasal [16,17], and intramuscular routes [18], to decrease the hemodynamic response to laryngoscopy and intubation. However, intravenous administration may cause bradycardia and hypotension and intranasal administration may be associated with irritation [19].

Nebulized dexmedetomidine, administered in doses of 1 and 2 µg/kg has been found to be an effective premedication in pediatric patients [19,20]. Nebulized dexmedetomidine may offer an attractive alternative to both intravenous as well as intranasal routes of administration, since the drug deposition following nebulization takes place over nasal, buccal as well as respiratory mucosa [19,20]. To the best of the authors’ knowledge, there are no studies demonstrating the effect of nebulized dexmedetomidine on the hemodynamic response to laryngoscopy and intubation.

Thus, the primary aim of this study was to evaluate the effect of preoperative dexmedetomidine nebulization (1 µg/kg) on the heart rate response to laryngoscopy and intubation in adult patients. The secondary aims were to evaluate the effects of nebulized dexmedetomidine on the systolic blood pressure response following laryngoscopy and intubation; intraoperative anesthetic and
analgesic consumption; time to extubation; and the 2-hr incidence of postoperative nausea and vomiting (PONV) and sore-throat.
Materials and Methods

Study design

The study was designed as a randomized, double-blinded, placebo controlled, parallel arm clinical trial.

Study participants

The study was carried out in ASA I & II adult patients, 18–60 years, of either gender, posted for elective short duration non-cardiac, non-neurosurgical operations requiring general anesthesia and tracheal intubation.

Study approval and trial registration

Institutional Ethics Committee approved the study (T/IM-NF/Anaesth/18/44) and written informed consent was obtained from each participant. The study was registered prospectively in the Clinical Trials Registry of India (CTRI) (trial registration number: CTRI/2019/01/017060; trial registration date: 14/01/2019; Principal Investigator: Dr. Satyajeet Misra).

Exclusion criteria

Patients undergoing emergency surgeries; obese patients (body mass index > 30 kg/m²); known or unanticipated difficult intubation; requiring more than 15 seconds or 2 attempts at laryngoscopy; rhythms other than sinus; patients on anti-hypertensive medications; known allergy to dexmedetomidine; or those on preoperative drugs that could be potential confounders (clonidine, gabapentin, pregabalin, steroids) were excluded from the study.

Randomization and allocation concealment
Patients were randomized into 2 equal groups by generating randomization codes following simple randomization technique using a software.

Group 1 (saline): patients received 0.9% saline nebulization (3–4 ml), 30 minutes before induction of anesthesia.

Group 2 (dexmedetomidine): patients received 1 µg/kg of dexmedetomidine nebulization diluted in 3–4 ml of 0.9% saline, 30 minutes before induction of anesthesia.

Allocation concealment was with sealed opaque envelopes which were opened once patients were received in the preoperative holding area on the day of surgery.

Nebulization procedure

The drugs for nebulization (saline or dexmedetomidine) were prepared and administered by an independent investigator in the preoperative holding area. Nebulization was carried out with an electrical compressor nebuliser (Eco Smart, Saify Healthcare and Medi Devices, India) capable of creating a fine mist till the entire volume was dispersed and this usually took 15–20 minutes. It was stopped when there was no further mist on tapping the volume chamber. The investigator oversaw the entire nebulization procedure and took no further part in the study. However, the investigator was authorized to intervene if the patients developed bradycardia, experienced increased sedation or decreases in peripheral oxygen saturation. In such an event, the nebulization was to be stopped and the patient treated accordingly.

Anesthesia protocol

Induction of anesthesia was carried out with 10 mg bolus aliquots of propofol titrated to loss of verbal response after premedication with intravenous ondansetron 4 mg, midazolam 1 mg and fentanyl (2 µg/kg). After achieving adequate bag mask ventilation, patients were paralyzed with
intubating dose of inj. vecuronium bromide (0.15 mg/kg). Depth of anesthesia was achieved with isoflurane in 50% air-oxygen mixture to maintain bi-spectral index (BIS; BIS Quatro, Covidien, USA) of 50–60; BIS sensors were applied before anesthesia induction. Ventilation was adjusted to maintain end-tidal carbon-dioxide at 32–35 mmHg.

Administration of additional doses of fentanyl were to be given if > 20% increase in heart rate and/or systolic blood pressure occurred from pre-induction baseline during the conduct of surgery. Fluid administration was as per consultants’ practice.

Laryngoscopy and intubation were carried out by the investigators with more than a decade of anesthetic practice. Increases in blood pressure in the 10-minute interval following laryngoscopy and intubation were treated with small aliquots of propofol (20–30 mg) while decreases in blood pressure and heart rate were treated with inj. ephedrine (6 mg) and inj. atropine (0.6 mg) respectively.

Following surgery, neuromuscular blockade was antagonised with inj. neostigmine (0.05 mg/kg) and inj. glycopyrrolate (0.02 mg/kg). The trachea was extubated once the patient was able to follow verbal commands. Patients were kept in the postoperative care unit for further 3 hours and discharged to the ward once they met the criteria for discharge.

**Primary aim and outcome parameters**

The primary aim was to study the heart rate changes following laryngoscopy and intubation in the two groups and as such, heart rate was measured at various time points; before administration of nebulization, after nebulization but before induction (baseline) and at every one minute interval till 10 minutes following laryngoscopy.

**Secondary aims and outcome parameters**
The secondary aims were to study the non-invasive systolic blood pressure changes following laryngoscopy and intubation; intraoperative anesthetic and analgesic consumption; time to extubation and the 2-hr incidence of PONV and sore-throat. Blood pressure measurements were performed at the same time points as the heart rate. The induction dose of propofol, total dose of intraoperative fentanyl and mean minimum alveolar concentration (MAC) of isoflurane were recorded for each patient. The response to skin incision was noted and recorded as a binary “yes/no response” (if < 20% changes in heart rate and/or systolic blood pressure- no; if > 20% changes in heart rate and/or systolic blood pressure-yes). If a positive response to skin incision was present, inj. fentanyl (1 µg/kg) was repeated. The time to extubation in minutes (from administration of neostigmine to removal of the tracheal tube) was noted in both the groups. The peripheral oxygen saturation and sedation scores (modified observer’s assessment of alertness/sedation scale) [21], were also recorded before and after nebulization for each patient.

PONV (subjective feeling of the urge to vomit or retching and/or vomiting) was assessed at 2-hr after surgery. Similarly, postoperative sore-throat (subjective feeling of irritation, discomfort or lump or pain in throat) was enquired at 2-hr after surgery, when patients would have recovered from the effect of anesthetic agents. Both were recorded as present or absent, but their severity was not assessed. All the outcome parameters were recorded by the investigator/s-in-charge of the case.

Sample size calculation

Assuming that there would be a 20% difference in the maximum heart rate between the two groups following laryngoscopy, 50 patients in each group were required to power the study to 80% to detect the difference with an alpha error of 5% (2-tailed). The pooled standard deviation assumed was 35. Accounting for 20% drop-outs after recruitment (unanticipated difficult intubation; requiring more than 15 seconds or 2 laryngoscopy attempts; protocol violation), we
aimed to recruit 120 patients into the study. Continuous variables were expressed as means (standard deviation) and categorical variables were expressed as proportions. Linear mixed effect modelling was performed to test the difference in the trend of repeated measures data like heart rate and systolic blood pressure. The difference in continuous variables were analysed with independent t-test and categorical variables were tested with the Chi-square test or the Fisher’s exact test as appropriate. Statistical analyses were performed with R 3.5 (R foundation, Vienna, Austria).
Results

A total of 120 patients were enrolled into the study over a one-year period (Study start date: 15/01/2019; end date: 09/01/2020) (Fig. 1; consort diagram). We did not encounter any attrition/drop-out after patient enrollment due to unanticipated difficult intubation, repeated or prolonged laryngoscopy or protocol violation. Patient demographics are presented in Table 1. Surgeries were mostly short duration of approximately 2–3 hours (modified radical mastectomies; laparoscopic cholecystectomies; ileostomy closures; laparoscopic hysterectomies etc.).

Following nebulization, there were no differences in the pre-induction hemodynamics or sedation scores between the two groups. After laryngoscopy and intubation, linear mixed effect modelling showed a significantly lower trend of increase in heart rate in the dexmedetomidine group versus saline (P = 0.012; Fig. 2). However, there was no significant difference in the systolic blood pressure response between the two groups (P = 0.904; Fig. 3). The induction dose of propofol, consumption of intraoperative fentanyl and the mean isoflurane requirements were significantly less in the dexmedetomidine group versus saline (Table 3). Similarly, there was a significant difference in the skin incision response, with a more positive response to skin incision seen in the saline group (Table 3). There was no difference in the time to extubation, PONV or sore-throat between the two groups (Table 3). There were no adverse events related to dexmedetomidine nebulization like intra or postoperative bradycardia and hypotension.
Discussion

In this study, there was a significant effect of preoperative dexmedetomidine nebulization 1 µg/kg versus saline on the heart rate responses following laryngoscopy and intubation. Preoperative dexmedetomidine nebulization was also effective in reducing the intraoperative anesthetic and analgesic consumption. However, there was no effect of dexmedetomidine nebulization on the systolic blood pressure responses following laryngoscopy or on the incidence of early PONV or postoperative sore-throat.

Common reasons for the hemodynamic changes following laryngoscopy and intubation are elevation of epiglottis, difficulty in glottic visualization, displacement of tongue, duration of laryngoscopy and insertion of the tracheal tube [22]. Dexmedetomidine acts on various brain stem and medullary nuclei (nucleus tractus solitarius, lateral reticular nucleus) and the hypothalamus to decrease the sympathetic nervous activity and attenuate the hemodynamic response to laryngoscopy and intubation [23].

Various studies have investigated the effects of intravenous dexmedetomidine on the hemodynamic response to laryngoscopy and intubation [11-15, 23-26]. While doses of 1–2 µg/kg have been found to be effective in attenuating this hemodynamic response, they are associated with significant side effects like bradycardia, hypotension, or respiratory depression [24, 25]. Lawrence et al. [24], found that a single dose of 2 µg/kg dexmedetomidine caused a higher incidence of bradycardia and hypotension as compared to placebo. Similarly, Mahajan et al. [25], found that with the same depth of anesthesia, there was a significant fall in heart rate, systolic and diastolic blood pressures in the dexmedetomidine group (1 µg/kg) versus placebo, which lasted till 30 minutes following drug administration.

Our results are different from previous studies [24,25]. Although the increase in heart rate was significantly attenuated in the dexmedetomidine group versus saline following laryngoscopy, we
did not find any incidence of bradycardia. Additionally, there was no significant difference in the systolic blood pressure increases following laryngoscopy between the two groups. This can be explained by our route of administration. The bio-availability of dexmedetomidine via inhaled route is 65% through nasal mucosa and 82% through buccal mucosa [19]. This may be comparable to 0.5 µg/kg of an intravenous dose [17], and as previous studies have shown [23], such doses have only a modest effect on hemodynamics following laryngoscopy and intubation. Further reasons for a lack of effect of nebulized dexmedetomidine versus saline on the systolic blood pressure changes following laryngoscopy could be that since the depth of anesthesia was similar in both groups, a higher MAC of isoflurane in the saline group versus a lower MAC in the dexmedetomidine group may have led to similar blood pressure changes.

In our study, we found that nebulized dexmedetomidine reduced the induction dose of propofol as well as the intraoperative anesthetic and analgesic consumption. Although the duration of surgery was similar in both groups, a significant lower consumption of fentanyl was seen in the dexmedetomidine group despite patients undergoing a variety of surgery. In addition, we also noted a significant difference in the response to skin incision between the groups which may have been related to a better quality of analgesia in the dexmedetomidine group. Thus, the effect of nebulized dexmedetomidine is similar to intravenous dexmedetomidine on the intraoperative anesthetic and analgesic consumption [14, 24, 26].

Unlike Lawrence et al. [24], who found a significant effect of 2 µg/kg of intravenous dexmedetomidine on the baseline sedation, in our study, the levels of sedation following nebulization and before induction of anesthesia were not different from baseline in both the groups. This may be related to the dose of dexmedetomidine used in our study and the patient population studied. While Abdel-Ghaffar et al. [20], found good sedation with 2 µg/kg of nebulized dexmedetomidine in pre-school children undergoing bone marrow biopsy, Zanaty et al. [19], found
that in children undergoing outpatient dental surgery, doses of 1 µg/kg of nebulized
dexmedetomidine provided lower levels of sedation as compared to nebulized ketamine or their
combination (1 µg/kg dexmedetomidine + 1 mg ketamine). Thus, a higher dose of nebulized
dexmedetomidine may be required to achieve optimal sedation in adults.

While some studies have shown that supplemental dexmedetomidine administration was
effective in reducing early PONV [27], other workers have found a beneficial effect of
supplemental dexmedetomidine on early nausea but not vomiting [28]. The reduction in PONV due
to dexmedetomidine may be due to an opioid sparing action, or a sympatholytic effect, or a direct
antiemetic effect by activation of alpha-2 adrenoreceptors [28]. In our study however, we did not
find a significant difference in the early PONV between the two groups despite a lower
consumption of fentanyl in the dexmedetomidine group. There may be several reasons for this.
Our anesthetic protocol included pre-induction administration of ondansetron, the effect of which
would be expected to last 8 hours and thus, may have masked any effect of dexmedetomidine on
early PONV, since the surgeries were typically of short duration. Additionally, most studies which
have demonstrated an effect of dexmedetomidine on PONV were either administered as a bolus
dose at the end of surgery [27], or as continuous infusion [28] whereas we used only a single dose
administered before induction of anesthesia. Finally, our surgeries were mixed in nature and this
may have also impacted the incidence of PONV.

The incidence of postoperative sore-throat following tracheal intubation is 21–65% [29], and
ranks as the 8th most adverse event in the postoperative period [30]. Previous reports have
described the favorable effects of dexmedetomidine on dilatation of bronchi by relaxation of
smooth muscles secondary to a direct effect on peripheral alpha-2 adrenoreceptors [31], and thus,
we sought to investigate whether there is an effect of dexmedetomidine on the incidence of
postoperative sore-throat. We however did not find a beneficial effect of nebulized
dexmedetomidine on postoperative sore-throat.

Strengths of the study

No previous studies have evaluated the effects of dexmedetomidine administered via the
nebulized route on the hemodynamic response to laryngoscopy and intubation, intraoperative
anesthetic and analgesic requirements and other postoperative outcomes. Instead of using traditional
statistical measures like analysis of variance to test for the difference in hemodynamic parameters
which estimates fixed effects, we utilized the mixed effect modelling for repeated measures which
tests for both fixed and random effects, since the blood pressure or heart rate at any given minute
may be the function of the previous reading.

Limitations of the study

We evaluated a single dose of nebulized dexmedetomidine and are thus unable to comment
whether different doses will have different effect on hemodynamics. In addition, we did not have a
comparator intravenous arm which would have allowed us to compare the nebulized route of
administration with the systemic route but believe it is intuitive and with the objective of finding
better routes of administration, systemic administration may be avoided, especially in short duration
surgeries.

Conclusion

In conclusion, single dose of nebulized dexmedetomidine 1 µg/kg, administered 30 minutes
before induction of anesthesia significantly attenuated the increase in heart rate but not systolic
blood pressures after laryngoscopy and decreased the intraoperative anesthetic and analgesic
consumption versus saline without an increase in adverse effects. Nebulized dexmedetomidine may
represent a favorable alternative to the intravenous route in adult patients undergoing short duration surgeries.
References


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<th>Parameter</th>
<th>Saline group (n = 60)</th>
<th>Dexmedetomidine group (n = 60)</th>
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<td>Age (yr)</td>
<td>40.63 (12.01)</td>
<td>37.68 (10.47)</td>
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<tr>
<td>Weight (kg)</td>
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<td>57.95 (9.63)</td>
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<tr>
<td>ASA I/II</td>
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<td>36:24</td>
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<td>Male: Female</td>
<td>35: 25</td>
<td>37: 23</td>
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<td>Duration of surgery (min)</td>
<td>142.53 (67.4)</td>
<td>123 (66.43)</td>
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Data are represented in mean (SD) or number of patients. ASA- American society of Anesthesiologists.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Saline group (n = 60)</th>
<th>Dexmedetomidine group (n = 60)</th>
<th>P value (95% CI)</th>
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<tr>
<td>Induction dose of propofol (mg/kg)</td>
<td>1.9 (0.58)</td>
<td>1.48 (0.42)</td>
<td>P &lt; 0.001 (0.24-0.61)</td>
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<tr>
<td>Intraoperative fentanyl (µg/kg)</td>
<td>2.82 (0.87)</td>
<td>2.43 (0.68)</td>
<td>P = 0.007 (95% CI = 0.11-0.67)</td>
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<td>Isoflurane (mean MAC)</td>
<td>0.78 (0.18)</td>
<td>0.71 (0.16)</td>
<td>P = 0.013 (95% CI = 0.017-0.14)</td>
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<td>Response to skin incision (yes: no)</td>
<td>16:44</td>
<td>6:54</td>
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<td>Time to extubation following reversal of neuromuscular blockade (min)</td>
<td>3.67 (2.42)</td>
<td>3.5 (2.07)</td>
<td>P = 0.68 (95% CI = 0.64-0.98)</td>
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<td>PONV (yes: no)</td>
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<td>3:57</td>
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<tr>
<td>Postoperative sore-throat (yes: no)</td>
<td>6:54</td>
<td>4:56</td>
<td>P = 0.74</td>
</tr>
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</table>

Data are represented in mean (SD) or number of patients. MAC- minimum alveolar concentration; PONV- postoperative nausea and vomiting.
Figure legends

Fig. 1. Consort flow diagram showing the recruitment of patients in the study.
Fig. 2. Changes in heart rate in both the groups. Baseline represents the post-nebulization pre-induction period. Mixed effect modelling showed a significantly lower trend of increase in heart rate in the dexmedetomidine group versus saline (P = 0.012). Vertical bars represent standard error of mean.
Fig. 3. Changes in systolic blood pressure in both the groups. Baseline represents the post-nebulization pre-induction period. Mixed effect modelling showed no difference in the overall trend in the systolic blood pressure changes between the two groups during the study period (P = 0.904). Vertical bars represent standard error of mean.