Clinical study to evaluate the role of preoperative dexmedetomidine in attenuation of hemodynamic response to direct laryngoscopy and tracheal intubation

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ABSTRACT

Objectives: Dexmedetomidine, an \( \alpha 2 \) agonist, has been evaluated for its hypnotic, analgesic, and anxiolytic properties in the intraoperative period and critical care setting. However, data on the effect of dexmedetomidine on attenuation of pressor response to direct laryngoscopy and tracheal intubation are limited. We studied the effect of a single preinduction intravenous dose of dexmedetomidine of 0.5 \( \mu g/kg \) on hemodynamic responses to tracheal intubation, and dose requirements of anesthetics for induction and their adverse effects.

Methods: Eighty adult patients scheduled for elective surgery under general anesthesia requiring tracheal intubation were included. Patients were randomized into two groups: dexmedetomidine and placebo (\( n = 40 \) each). The study drug was administered intravenously over a period of 10 minutes prior to induction. Direct laryngoscopy and endotracheal intubation were performed. Hemodynamic parameters, the total dose of propofol, and adverse effects were recorded during induction and postintubation periods for 15 minutes.

Results: The maximum percentage increase in the heart rate after intubation was 19.6% less in the dexmedetomidine group than that in the placebo group (12.96% vs. 32.57%). The maximum percentage increases in systolic blood pressure, diastolic blood pressure, and mean blood pressure after intubation were significantly lower in the dexmedetomidine group than in the placebo group (12.38% vs. 45.63%, 19.36% vs. 60.36%, and 15.34% vs. 50.33%, respectively). There was a significant reduction of the mean total dose of propofol required for induction, 1.04 mg/kg in the dexmedetomidine group versus 2.01 mg/kg in the placebo group (\( p < 0.001 \)). No serious side effects or adverse reactions were observed in either group.

Conclusion: Administration of a single preinduction intravenous dose of dexmedetomidine of 0.5 \( \mu g/kg \) resulted in significant attenuation of the rise in the heart rate, systolic blood pressure, diastolic blood pressure, and mean blood pressure, until 5 minutes postintubation. It significantly reduced the dose requirements of propofol for induction and caused minimal side effects.

1. Introduction

Laryngoscopy and tracheal intubation (TI) may trigger reflex responses causing profound variation in cardiovascular physiology, and may cause serious complications in patients with underlying coronary artery disease, hypertension, or intracranial neuropathy. Various drugs have been used to attenuate these responses, but none have been entirely successful. Dexmedetomidine, the pharmacologically active d-isomer of medetomidine, is a selective \( \alpha 2 \)-adrenoceptor agonist. Its short half-life makes it an ideal drug for intravenous (IV) titration. Various studies have evaluated its hypnotic, analgesic, and anxiolytic properties in the intraoperative period and critical care setting.
setting. However, there are limited data on its effect on attenuation of pressor response to direct laryngoscopy and TI. Most of the studies have used higher doses of dexmedetomidine, 1–2 μg/kg; very few studies have evaluated the role of lower doses of dexmedetomidine (0.5–0.6 μg/kg) in attenuation of pressor responses. The purpose of this study was to evaluate the effects of a single preinduction IV dose of 0.5 μg/kg dexmedetomidine on hemodynamic response to TI, and dose requirements of propofol for induction and its adverse effects in adult patients undergoing surgery under general anesthesia.

2. Methods

After the protocol was approved by the Institutional Ethics Committee (Government Medical College, Chandigarh, India) and written informed consent was obtained, 80 adult patients of either sex, American Society of Anesthesiologists (ASA) physical status I/II, in the age group of 18–60 years, who were scheduled to undergo elective surgery under general anesthesia requiring TI, were included in this study. The Clinical Trials Registry of India registered this intervention trial (registration number: CTRI/2013/08/003855). The exclusion criteria were as follows: anticipated difficulty in airway, body mass index > 30 kg/m², preoperative medication with clonidine or alpha methyldopa, hiatus hernia, gastroesophageal reflux, known allergy to dexmedetomidine, and known case of coronary artery disease.

The study design was prospective, randomized, double blind, and placebo controlled. Using a computer-generated random-number table, patients were randomly allocated to either the dexmedetomidine group (n = 40) or the placebo group (n = 40). Allocation concealment was performed using sequentially numbered, coded, sealed envelopes. The study drugs were prepared in identical-looking syringes by an independent investigator who was not involved in the recording of observations. The contents of syringes were unknown to the anesthesiologist involved in the administration of the drug and recording of observations. Decoding was performed on completion of the study.

Patients were premedicated with oral alprazolam 0.25 mg and kept fasting for 6 hours prior to surgery. In the operating room, standard monitoring [pulse oximetry, noninvasive arterial blood pressure, electrocardiography, and capnography (S/5: Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland)] was applied, and baseline parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and arterial oxygen saturation (SpO2) were recorded. After securing IV access, the study drug was administered over a period of 10 minutes as per group allocation using a syringe infusion pump (EMCO Meditek Pvt Ltd, Mumbai, India).

The study drug dexmedetomidine (Dexem; Themis Medicare Limited, Mumbai, India) was prepared as a 20 mL solution with a concentration of 0.5 μg/mL. This concentration was achieved by diluting 100 μg of dexmedetomidine in 20 mL of 0.9% normal saline. In addition, 20 mL of 0.9% normal saline was prepared for the placebo group in identical-looking syringes. Thereafter, the independent investigator calculated the volume of dexmedetomidine (0.5 μg/kg) to be administered, according to the weight of the patients. The volume of 0.9% normal saline to be infused in placebo group was kept equivalent to the volume of the dexmedetomidine drug infusion (as per calculation of dose 0.5 μg kg⁻¹) prepared for dexmedetomidine group. The anesthesiologist administering the study drug was blinded to the contents of the identical-looking syringes. Only the independent investigator who prepared the drug was aware of the contents of the syringes, and he or she directed the anesthesiologist to infuse a particular volume of the study drug/placebo as per group allocation.

Five minutes after the administration of the study drug, all patients received IV glycopyrrolate 0.2 mg and fentanyl 2 μg/kg. After preoxygenation for 3 minutes, anesthesia was induced with a manual bolus injection of 1% propofol until the loss of verbal contact. Neuromuscular blockade was achieved with vecuronium bromide 0.1 mg/kg, and the patient's lungs were manually ventilated for over 3 minutes with 67% nitrous oxide in oxygen. After 3 minutes, direct laryngoscopy was performed with a Macintosh laryngoscope, followed by TI with a cuffed endotracheal tube of appropriate size. The ventilator setting was adjusted to achieve SpO₂ of ≥ 95% and end-tidal carbon dioxide (EtCO₂) of 30–35 mmHg. Anaesthesia was maintained with nitrous oxide–oxygen combination (67%;33%), intermittent bolus administration of fentanyl (20 μg IV) and vecuronium (0.02 mg/kg IV), as and when required during surgery. NB: Fentanyl (20 μg/kg IV) is a higher dosage and was not administered as bolus during the surgical period in our study. Rate-controlled infusion of propofol was initiated with a manual rate-adjustment pump following the 10–8–6 manual infusion scheme. Roberts et al formulated and validated the aforesaid regimen based on pharmacokinetic predictions, and found that by following this manual infusion scheme, the blood propofol concentration of 3 μg/mL can be achieved within 2 minutes and maintained for 40 for and 90 minutes without which is adequate for achieving surgical anesthesia when combined with nitrous oxide. Hypotension (SBP < 70 mmHg) was managed with 5 mg ephedrine IV. In the event of bradycardia (HR < 40 bpm), 0.5 mg of atropine was administered IV. At the end of surgery, all the patients received IV dicyclofenac sodium 1 mg/kg for over 30 minutes and ondansetron 0.1 mg/kg, to reduce pain and emesis, respectively. After completion of surgery, anesthesia was discontinued, and residual neuromuscular blockade was antagonized with neostigmine and glycopyrrolate in the doses of 0.05 mg/kg and 0.01 mg/kg, respectively. Once awake and responsive, the patient was extubated and shifted to the postanaesthesia care unit. HR, SBP, DBP, MBP, SpO₂, and EtCO₂ were continuously monitored and recorded before infusion of the study drug (T0: baseline), after completion of infusion (T1), at 5 minutes (T2), after induction (T3), just before intubation (T4), and after intubation at 1-minute (T5), 3-minute (T6), 5-minute (T7), 10-minute (T8), and 15-minute (T9) intervals. After recording the observations for 15 minutes, the rest of the anesthetic procedure was carried out at the discretion of the attending anesthesiologist. During the study, the total dose of propofol required for induction was recorded. Side effects of the study drugs, if any, were also recorded. Cases were excluded from the study if there was inadequate jaw relaxation, Cormack–Lehane grade > 2, the patient moved or bucked during laryngoscopy or intubation, or the number of attempts for intubation was > 1.

All quantitative variables were estimated using measures of central location (mean and median) and measures of dispersion (standard deviation and standard error). Normality of data was checked by measures of skewness and Kolmogorov–Smirnov tests of normality. Demographic data were analyzed by Student t test and Chi-square test. Analysis of variance was used to analyze changes over time. When statistical significance was found, the difference between two different data for each variable was analyzed by post hoc multiple comparison test with Bonferroni’s correction. Intergroup comparisons for hemodynamic parameters were performed with t test. Power analysis was carried out by statistical software package (SPSS, version 15.0 for Windows; SPSS Inc., Chicago, IL, USA). A sample size of 40 patients per group was required to detect a 15% change in HR, SBP, DBP, and MAP between baseline and postintubation, with a power of 90% at the 5% significance level. All data were expressed as mean ± standard deviation (95% confidence intervals) and p < 0.05 was considered significant.
3. Results

Figure 1 shows the flow diagram for this study, in which 85 patients were assessed for eligibility and 80 adult patients were included in the study. The results of 80 adult patients were analyzed.

Table 1 shows the demographic characteristics of the patients, which were comparable between the dexmedetomidine and the placebo groups. Baseline hemodynamic parameters were comparable between the two groups. Five minutes after the infusion of the study drug, we observed a significant fall in HR and blood pressure in the dexmedetomidine group as compared to the placebo group (p < 0.001).

In the placebo group, there was a statistically significant increase in the HR at 1 minute and 3 minutes after intubation from the baseline value (29.15% and 16.20%, respectively), which stabilized after 10 minutes. On the contrary, in the dexmedetomidine group, we observed 10.31% and 11.77% decreases in the HR from the baseline value at 1 minute and 3 minutes after intubation, respectively. Thereafter, the HR came to near baseline in the placebo group, but it remained persistently lower in the dexmedetomidine group (p < 0.001). On intergroup comparison, a significant difference in the HR was observed between the two groups at all time points, which persisted until 15 minutes post-intubation (Figure 2).

In the dexmedetomidine group, a slight increase was observed in SBP, DBP, and MBP after intubation when compared to pre-intubation values; however, when compared to baseline, there was a statistically significant decrease in blood pressure postintubation, which persisted for 5 minutes (p < 0.001). However, in the placebo group, there was a significant increase in SBP, DBP, and MBP after intubation compared to both baseline and preintubation values, typically seen at 1 minute after TI, after which these returned to values comparable to baseline. On intergroup comparison, a significant difference in the blood pressure was observed between the two groups at 1 minute, 3 minutes, and 5 minutes after TI (p < 0.001), which became insignificant at 10 minutes and 15 minutes postintubation (Figures 3–5).

The differences in the mean values of SpO2 and EtCO2 between the two groups at all time points were statistically insignificant (p > 0.05). SpO2 was never < 95% in either group during the entire study period.

The mean total doses of required propofol for induction in the dexmedetomidine and placebo groups were 60.75 ± 12.483 mg and 118.00 ± 16.361 mg, respectively, which were equivalent to 1.04 mg/kg and 2.01 mg/kg, respectively. The difference in the mean doses of propofol between the two groups was statistically significant (p < 0.001).

None of the patients in either group had any significant adverse events such as bradycardia, respiratory depression, or hypotension, except one patient in the dexmedetomidine group who had hypotension and responded to ephedrine 6 mg IV.

![Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the patients included in the study.](image)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic characteristics of patients receiving dexmedetomidine or placebo prior to induction of general anesthesia.</th>
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<tbody>
<tr>
<td></td>
<td>Dexmedetomidine (n = 40)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>35.68 ± 10.3</td>
</tr>
<tr>
<td>Male:female</td>
<td>9:31</td>
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<tr>
<td>Weight (kg)</td>
<td>58.18 ± 10.7</td>
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</tbody>
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Data are presented as mean ± standard deviation or n (proportion).
4. Discussion

The results of the present study show that the preinduction administration of a single dose of dexmedetomidine of 0.5 μg/kg IV resulted in significant attenuation of cardiovascular responses to laryngoscopy and TI. In contrast to the previous studies where dexmedetomidine in a dose range of 1–2 mg/kg was used, we decided to use 0.5 mg/kg because, in a preliminary study using a dose of 1 mg/kg, we observed significant bradycardia and hypotension requiring pharmacological intervention in the majority of our patients. A search of the available literature revealed few studies evaluating the role of lower doses of dexmedetomidine (0.5–0.6 mg/kg) in attenuation of pressor responses.

Dexmedetomidine has been shown to distinctly portray nonlinear concentration-dependent pharmacokinetics leading to a biphasic blood pressure response. At a higher concentration following a bolus administration, it stimulates peripheral α2 receptors of vascular smooth muscles, causing a transient increase in blood pressure and systemic vascular resistance. Afterward, as the concentration decays, the central sympatholytic effect (acting on the brainstem, medullary nuclei, and hypothalamus) predominates by activation of postjunctional vascular α2 receptors, causing a decrease in blood pressure and cardiac output. It also causes bradycardia due to central sympatholysis with a resultant unopposed vagal tone and possibly due to presynaptic-mediated diminution of noradrenaline release. In our study, dexmedetomidine was administered as a single low-dose infusion (0.5 μg/kg) over a period of 10 minutes. We avoided bolus administration of the study drug and preferred slow infusion, to circumvent the initial undesirable vasoconstrictor effects. We observed that by administering the drug as a continuous infusion over a definite and prolong period of time, this initial hemodynamic response can be abolished.

In the present study, in the dexmedetomidine group, the HR was significantly lower than the baseline values at all time intervals of the study (pre- and postinduction, and up to 15 minutes postintubation), compared to the placebo group. Remarkably, the maximum percentage increases in the HR from the preintubation values seen at 1 minute and 3 minutes were, respectively, 19.6% and 8.14% less in the dexmedetomidine group, as compared to the placebo group (12.96% and 11.23% in the dexmedetomidine group vs. 32.57% and 19.37% in the placebo group, respectively). This significant attenuation of rise in the HR in response to TI persisted until 3 minutes postintubation; thereafter, the results were comparable in both intra- and intergroup comparison.

In the dexmedetomidine group, SBP, DBP, and MBP were significantly lower than the baseline values at all time intervals of the study (pre- and postinduction, and up to 15 minutes postintubation), whereas there was a significant rise in SBP, MBP, and DBP 1 minute postintubation in the placebo group. The maximum percentage increases in SBP, DBP, and MBP at 1 minute postintubation were significantly lesser in the dexmedetomidine group than in the placebo group, thereby showing that dexmedetomidine significantly attenuated the pressor response that was observed until 5 minutes postintubation. Pressor response to TI is attributed

![Figure 2. HR course of the dexmedetomidine (---) and placebo (-----) groups. * p < 0.001, significant increase in the HR at 1 minute (T5) and 3 minutes (T6) postintubation in the placebo group from the baseline values. ** p < 0.001, significant decrease in the HR at 1 minute (T5) and 3 minutes (T6) postintubation in the dexmedetomidine group from the baseline values. *** p < 0.001, significant difference in the HRs between the two groups until 15 minutes postintubation. **** p < 0.001, significant fall in the HR in the dexmedetomidine group as compared to the placebo group, 5 minutes after infusion of drug (T2). HR = hear rate.](image)
to the rise in plasma catecholamine, with the concentration being maximum at 1 minute and persisting for 3 minutes,30,31 and we observed significant attenuation of this response with a lower dose of dexmedetomidine.

Various studies have used higher dosages of dexmedetomidine (1–2 μg/kg) and observed significant attenuation of pressor response to TI.9–19,32 Many among the aforesaid studies consistently reported biphasic response of initial transient hypertension (vasoconstrictive effect of drug) followed later by severe hypotension and bradycardia (central sympatholytic effects)28,29 and/or respiratory depression (action on postsynaptic α2-adrenoceptors located in the locus coeruleus).9,10,14,22,33 Kunisawa et al11 administered dexmedetomidine as an initial dose (1.0 μg/kg for 10 minutes), followed by a continuous infusion (0.7 μg/kg/h) for 15 minutes prior to induction. Remarkably, they did not observe any significant hypotension or bradycardia, or difference in the frequencies of pharmacological interventions in any of the three study groups, which might be because of factors such as the stringent criterion for administration of a vasoactive agent (SBP < 70 mmHg) or the lack of any premedication drugs.11 Bajwa et al14 observed a fall in oxygen saturation up to 94–95% in the dexmedetomidine group, after the completion of dexmedetomidine infusion (1 μg/kg in 20 minutes). Yildiz et al10 observed significant sedation (with a short period of apnea in 3 cases) and a fall in SpO2 values immediately after drug infusion (1 μg/kg in 5 minutes), although SpO2 values remained > 95% at all time intervals. Lawrence et al9 administered a single preinduction IV dose of dexmedetomidine of 2 μg/kg (given over 5 minutes), and observed that most of the patients, who also received atropine premedication, were deeply sedated (Ramsay score 4–5) and had a higher incidence of hypotension and bradycardia.

Very few investigators have studied the effect of smaller doses of dexmedetomidine (0.5–0.6 μg/kg IV) on sympathoadrenal responses after TI.20–23 Results of the present study are in agreement with these studies that reported that after TI, the maximum increases in SBP, DBP, and HR were significantly lesser with lower doses of dexmedetomidine.20,21,23 In addition, Jaakola et al21 also reported a significant reduction in plasma noradrenaline concentration when compared to the placebo group. Sulaiman et al23 also observed similar results while evaluating the effects of a single low dose of dexmedetomidine (0.5 μg/kg, slow IV infusion for 10 minutes, 15 minutes prior to TI) in patients with coronary artery disease, undergoing off-pump coronary artery bypass grafting.

In the present study, dexmedetomidine was well tolerated in smaller dosages, and no serious side effects or adverse reactions were noticed. We observed hypotension in only one patient in the dexmedetomidine group, which required pharmacological intervention. The ventilatory parameters (SpO2 and EtCO2) were also comparable between the two groups, and at no time, SpO2 fell below 95% in either group, indicating the safety profile of continuous infusion of low-dose dexmedetomidine. Our results are in accordance with previous studies using similar low-dose infusions of dexmedetomidine.20–23

Dexmedetomidine has a unique property of causing sedation by acting on postsynaptic α2 subtype adrenoceptors located in the locus coeruleus, resulting in a decrease in noradrenergic activity.29 The sedative and anesthetic sparing effects of the drug have been studied extensively and utilized in anesthesia practice.5,34–39 The
Figure 4. DBP course of the dexmedetomidine (---) and placebo (-----) groups. * \( p < 0.001 \), significant increase in DBP in placebo group at 1-minute postintubation (T5) compared to baseline value. ** \( p < 0.001 \), significant decrease in DBP in the dexmedetomidine group until 5 minutes postintubation (T5, T6, and T7) compared to baseline values. *** \( p < 0.001 \), significant difference in the DBP observed between the two groups until 5 minutes postintubation (T5, T6, and T7). DBP = diastolic blood pressure; T5 = 1 minute after intubation; T6 = 3 minutes after intubation; T7 = 5 minutes after intubation.

Figure 5. MBP course of the dexmedetomidine (---) and placebo (-----) groups. * \( p < 0.001 \), significant increase in MBP in the placebo group at 1 minute postintubation (T5) compared to baseline value. ** \( p < 0.001 \), significant decrease in MBP in the dexmedetomidine group until 5 minutes postintubation (T5, T6, and T7) compared to baseline values. *** \( p < 0.001 \), significant difference in the MBP observed between the two groups until 5 minutes postintubation (T5, T6, and T7). MBP = mean blood pressure; T5 = 1 minute after intubation; T6 = 3 minutes after intubation; T7 = 5 minutes after intubation.
The present study showed that administration of a single dose of dexmedetomidine (0.5 μg/kg IV) resulted in a significant reduction in the doses of propofol required for induction, 1.04 mg/kg in the dexmedetomidine group versus 2.01 mg/kg in the placebo group. Previous studies using similar doses of dexmedetomidine showed significant reductions in the induction dose of thiopentone and intraoperative opioid requirements.19,20–22 Although very few studies have observed the effect of dexmedetomidine on the reduction of propofol dosage required for induction of anesthesia, they observed similar results.15,19 A recent study by Liu et al.10 reported that a single dose of dexmedetomidine of 0.5 μg/kg IV can significantly reduce the mean propofol effect site concentration (guided by Narcotrend index), without any undesirable hemodynamic variations. Our study has certain limitations. Dexmedetomidine may be useful in high-risk cardiac patients; however, the present study included only patients with ASA physical status I and II. In addition, measurement of QT interval and plasma catecholamine levels are included only patients with ASA physical status I and II. In addition, (guided by Narcotrend index), without any undesirable hemodynamic variations.

We conclude that a single dose of 0.5 μg/kg dexmedetomidine given over a period of 10 minutes prior to the induction of anesthesia significantly attenuated the hemodynamic responses associated with laryngoscopy and intubation, and this dose was as effective as the 1 μg/kg dose reported in the literature. It also reduced the dose of propofol required for induction and was not associated with any significant adverse effects. We feel that large-scale studies investigating the myocardial protecting properties of dexmedetomidine during induction and intubation may be required in different patient populations.

References