Comparison of the efficacy of two doses of dexmedetomidine in attenuating the hemodynamic response to intubation in patients undergoing elective cardiac surgery: A randomized double-blinded study

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Abstract

**Background and Aims:** Transient tachycardia and hypertension associated with laryngoscopy and intubation may be hazardous to patients presenting for cardiac surgery. The α₂ agonist dexmedetomidine may blunt this stress response, but the optimal dose which will accomplish this without causing hypotension and bradycardia is not well established. The primary objective of this study was to compare the efficacy of two doses of dexmedetomidine (0.5 and 1 µg/kg) as a 15 min infusion in attenuating the hemodynamic stress response to laryngoscopy and endotracheal intubation in elective cardiac surgery.

**Material and Methods:** Seventy six patients scheduled for elective cardiac surgery received a single preoperative dose of dexmedetomidine of either 0.5 µg/kg (low dose) or 1 µg/kg (high dose) as a 15‑min infusion prior to induction. The hemodynamic response to laryngoscopy and endotracheal intubation (heart rate, systolic blood pressure, mean arterial pressure, and diastolic blood pressure) were recorded at different times. Independent sample t-test, Chi-square test of association, and repeated measures analysis of variance were used to analyze the collected data.

**Results:** The incidence of hypertension following intubation was significantly more in the low‑dose group. Administration of 1 µg/kg dexmedetomidine was not accompanied by hypotension or bradycardia.

**Conclusion:** Dexmedetomidine in a dose of 1 µg/kg is more effective than 0.5 µg/kg for attenuation of hemodynamic stress response to intubation in cardiac surgery. A more graded increase in the dose of dexmedetomidine may lead to an optimum dose in attenuating the hemodynamic response to intubation.

**Keywords:** α₂ agonist, cardiac surgery, dexmedetomidine, endotracheal intubation, laryngoscopy, stress response

Introduction

Laryngoscopy and endotracheal intubation may cause tachycardia, hypertension, and arrhythmias associated with significant increase in plasma concentrations of catecholamines. This sympathoadrenal response may precipitate myocardial ischemia in patients presenting for cardiac surgery due to their poor cardiac reserve.[1]

The α₂ agonist dexmedetomidine can decrease sympathetic tone and blunt the hemodynamic responses to noxious stimulation.[2] However, there is a dose-related increased risk of bradycardia and hypotension, which may be poorly tolerated in cardiac patients who are already on rate control drugs such as β-blockers.[3,4]

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The primary objective of this study was to compare the efficacy of two different doses of dexmedetomidine (0.5 and 1 µg/kg) given preoperatively as a 15-min infusion in attenuating the hemodynamic response to endotracheal intubation in patients undergoing elective cardiac surgery.

**Material and Methods**

This was a prospective, double-blind, randomized study comparing the effect of two different doses of dexmedetomidine in patients undergoing elective cardiac surgeries. After institutional review board and Ethics committee approval, 76 patients aged >18 years, scheduled for elective cardiac surgery, who gave informed consent, were enrolled for the study over a 1-year period.

Patients with left ventricle ejection fraction <40%, left main coronary artery occlusion >50%, moderate to severe valvular dysfunction, preoperative medication with clonidine or α methylldopa, preoperative arrhythmias or bradycardia (HR <50/min), preoperative left bundle branch block, intubation attempt lasting longer than 15 s, and anticipated difficult intubation were excluded from the study.

All patients received detailed oral and written information during the preanesthetic consultation and gave written informed consent.

β-blockers and calcium channel blockers were continued perioperatively. Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers were stopped 2 days prior to surgery. Diuretics were withheld on the morning of surgery. All patients were premedicated with oral alprazolam 0.25 mg and oral pantoprazole 40 mg the night and 2 h before the surgery.

Intraoperative monitoring included five lead electrocardiogram, pulse oximetry, capnogram, continuous invasive arterial pressure, central venous pressure (CVP), urinary output, nasal temperature, bispectral index (BIS), and trans-esophageal echocardiography.

Patients were randomly allocated into one of the two groups by a computer-generated randomization table. Allocation concealment was performed using sequentially numbered, coded, sealed envelopes. Dexmedetomidine infusion was commenced in a double-blinded fashion through syringe pump.

Patients received 0.5 and 1 µg/kg intravenous (IV) dexmedetomidine over 15 min in group D1 and D2 respectively, five min before induction of general anesthesia. Anesthesia was induced with IV etomidate (0.2–0.3 mg/kg) and IV fentanyl (2–3 µg/kg). Loss of eye lash reflex and lack of response to verbal commands were checked during induction. BIS <60 was considered as the end point of induction. Rocuronium 1 mg/kg was administered intravenously to facilitate endotracheal intubation. Each intubation was performed by an experienced anesthesiologist and accomplished within 15 s. Anesthesia was maintained after intubation with sevoflurane 1%, IV fentanyl 1–2 µg/kg, and muscle relaxant IV vecuronium 0.02 mg/kg repeated every 30 min.

Systolic and diastolic blood pressure (SBP, DBP), mean arterial pressure (MAP), and heart rate (HR) were recorded at baseline (t0); 5 min after end of study drug infusion (t1); 2 min after administering the induction agents (t2); and at 1 (t3), 3 (t4), and 5 min (t5) after the endotracheal intubation.

Ramsay Sedation Score was recorded at baseline, at 5 min of drug infusion and at the end of drug infusion. BIS was recorded at intubation and 10 min after intubation.

The incidence of hypotension, hypertension, bradycardia, and tachycardia, following laryngoscopy and intubation were recorded in the data collection forms.

**Protocol to treat hemodynamic deviations following laryngoscopy and intubation**

Hypertension (defined as SBP ≥30% above baseline or SBP >160 mmHg) was treated with bolus doses of fentanyl 1 µg/kg IV. Tachycardia associated with hypertension was treated with esmolol in 0.5 mg/kg IV increments until effect. Hypotension (defined as either SBP ≤30% below baseline or SBP <90 mm Hg) was treated in a stepwise manner with IV fluids to keep CVP within 2 mm Hg of baseline, Inj phenylephrine (20 µg/mL IV) bolus or Inj ephedrine 3 mg/mL and adrenaline infusion. Bradycardia (defined as heart rate <40/min) was treated with Inj atropine 0.6 mg IV increments until effect. Tachycardia (without hypertension) (defined as HR >100/min) was treated with IV fluids to keep CVP within 2 mmHg of baseline and esmolol in 0.5 mg/kg increments until effect.

**Statistical analysis**

Keeping the precision of estimates of outcome statistics as 95% confidence limits with a power of 80% and on the basis of previously published study, sample size was calculated as 38 per group.\[^{[5]}\]

Independent sample t-test, repeated measures analysis of variance (ANOVA), and chi-square test of association were
used for statistical analysis. In all the analyses, the significance level was taken to be 0.05. All the tests were two-tailed. Statistical analysis was carried out using the statistical package, SPSS (version 22.0.0.0).

Results

The demographic data were comparable in the two groups [Table 1]. The two groups were comparable in the incidence of comorbidities and preoperative drug treatment [Table 2].

Using Chi-square test of association, the two groups were found to be comparable for risk factors, such as hypertension, diabetes mellitus and old history of myocardial infarction [Table 2]. The two groups D1 and D2 were also comparable with respect to preoperative drug usage (beta-blockers, Calcium channel blockers, Angiotensin receptor blockers/Angiotensin converting enzyme inhibitors, and diuretics).

The mean values of BIS at intubation, sedation at baseline, 5 min through the drug and infusion and at the end of drug infusion were statistically comparable [Table 3].

HR, SBP, DBP, and MAP were maximum after 1 min of intubation in both the groups [Figure 1].

Hypertension occurred in 14 patients in group D1 and 4 in group D2 (Chi-square, \( P = 0.017 \)). Hypotension occurred in one patient in each group. There was no incidence of bradycardia or tachycardia in either group.

Discussion

Hypertension, arrhythmias, and myocardial ischemia induced by direct laryngoscopy and endotracheal intubation can be catastrophic in cardiac surgical patients. Opioids, β-blockers, local anesthetics, vasodilators, calcium channel blockers, and α adrenergic agonists have been used to attenuate the pressor response to intubation.

The α adrenergic agonist dexmedetomidine can be used to provide cooperative sedation, analgesia, sympatholysis, and cardiovascular stability while avoiding respiratory depression.\(^6\) Similar to the studies by Pathak et al. and Keniya et al., we were able to induce sedation mimicking natural sleep and quick arousal with both study doses of dexmedetomidine. There was no join the words with a hyphen requiring intervention to maintain airway.\(^7,8\)

| Table 1: Independent sample t-test for demographic and baseline characteristics |
|-----------|-----------|-----------|
| Group    | Mean (standard deviation) |
|-----------|--------------------------|
| Age       | D1 57.9 (8.5) D2 56.8 (8.6) |
| Weight    | D1 63.8 (8.4) D2 61.2 (7.6) |
| Height    | D1 162.7 (6.1) D2 161.7 (6.8) |
| BMI       | D1 24.1 (2.7) D2 23.4 (2.4) |
| Ejection fraction | D1 56.7 (9) D2 58.3 (8.6) |
| ASA grade | D1 3.053 (0.2) D2 3.053 (0.2) |
| Number of diseased arteries | D1 2.868 (0.3) D2 2.895 (0.3) |
| Angina Grade | D1 2 (0.7) D2 2.1 (0.7) |
| Dyspnoea Grade | D1 1.7 (0.6) D2 1.8 (0.7) |

BMI=Body mass index, ASA=American Society of Anesthesiologists, D1=Dexmedetomidine 0.5 µg/kg IV over 15 min, D2=Dexmedetomidine 1 µg/kg IV over 15 min, n=Number of patients

| Table 2: Chi-square tests for risk factors, preoperative drug usage |
|-----------|-----------|-----------|
| Hypertension | D1 30 D2 29 |
| Diabetes mellitus | D1 24 D2 22 |
| Old myocardial infarction | D1 12 D2 13 |
| Beta-blockers | D1 35 D2 36 |
| Calcium channel blockers | D1 8 D2 7 |
| Angiotensin receptor blockers/angiotensin converting enzyme inhibitors | D1 9 D2 8 |
| Diuretics | D1 3 D2 4 |

D1=Dexmedetomidine 0.5 µg/kg IV over 15 min, D2=Dexmedetomidine 1 µg/kg IV over 15 min, n=Number of patients

| Table 3: Independent sample t-test for BIS and Ramsay sedation score |
|-----------|-----------|-----------|
| Group    | Mean (standard deviation) | P |
|-----------|--------------------------|---|
| BIS at intubation | D1 50.1 (1.9) D2 49.5 (2) | 0.206 |
| BIS 10 min after intubation | D1 48.9 (1.7) D2 48.3 (1.9) | 0.170 |
| Sedation score at baseline | D1 1.7 (0.4) D2 1.7 (0.4) | 1.000 |
| Sedation score after 5 min of drug infusion | D1 2.1 (0.4) D2 2.3 (0.4) | 0.787 |
| Sedation score at the end of drug infusion | D1 3 (0.2) D2 3.1 (0.2) | 0.562 |

BIS=Bispectral index. n=Number of patients, D1=Dexmedetomidine 0.5 µg/kg IV over 15 min, D2=Dexmedetomidine 1 µg/kg IV over 15 min
Despite strong evidence suggesting the efficacy of dexmedetomidine in attenuating intubation stress response, the best dosing strategy to achieve this goal in cardiac surgery patients is not yet clear.\cite{5,9} It has been established that stimulation of alpha-adrenoreceptors can be beneficial during myocardial ischemia. Dexmedetomidine can cause a reverse steal effect whereby the transmural redistribution of blood flow away from the ischemic endocardium is prevented by specific epicardial vasoconstrictive effects. It can also cause bradycardia thereby decreasing myocardial oxygen consumption.\cite{10} These properties make dexmedetomidine an ideal anesthetic adjuvant for coronary artery bypass grafting.

The hypotensive and negative chronotrophic effects of dexmedetomidine are theoretical concerns which could limit its use in previously β-blocked ischemic heart disease patients. There was no incidence of bradycardia requiring treatment in our study even though 71 out of the 76 patients enrolled in our study were on β-blockers. Sulaiman et al. and Sulhyan et al. also suggested dexmedetomidine administration even in patients receiving β-blockers.\cite{5,11} Similar results were obtained by Menda et al.\cite{12}

Bradycardia was observed at the first and fifth minute after dexmedetomidine administration by Lawrence et al.\cite{13} possibly due to bolus administration. In our study, dexmedetomidine was administered as an infusion over 15 min. The administration of a bolus dose of 1 µg/kg dexmedetomidine may result in an initial transient hypertension and reflex bradycardia followed by hypotension.\cite{14} The initial hypertensive response is probably due to α2 receptor stimulation of vascular smooth muscle. This response may be markedly decreased by slow infusion.\cite{14}

A linear increase in heart rate and mean arterial pressure has been observed during the first 45 s of laryngoscopy. Stoelting et al. noticed that when the duration of laryngoscopy was limited to 15 s, the cardiovascular responses were minimal.\cite{15} In our study, all intubations were performed by an experienced anesthesiologist and limited to <15 s. We also noted that, whatever be the dose used, heart rate and blood pressure were maximum at 1 min after intubation.

We have shown that dexmedetomidine 1 µg/kg is more effective than 0.5 µg/kg in attenuating hemodynamic response to endotracheal intubation. Our results are similar to those of Raval et al. and Smitha et al.\cite{16,17} Our results differ from those of Jairineshin et al., who did not find any difference between the two doses.\cite{18}
We did not include a placebo group because meta-analysis of randomized controlled trials has shown dexmedetomidine to be effective in attenuation of hemodynamic stress response to laryngoscopy and intubation as compared with placebo, and therefore, it appeared unnecessary to place patients in the placebo group.\[10\]

We did not measure plasma catecholamine levels which are a more objective means of evaluating stress response. The quality of intubation was not assessed. As this was a single center study, the external validity of our study is limited.

**Conclusion**

Dexmedetomidine in a dose of 1 µg/kg is more effective than 0.5 µg/kg for attenuation of hemodynamic stress response to intubation in cardiac surgery. A more graded increase in the dose of dexmedetomidine may lead to an optimum dose in attenuating the hemodynamic response to intubation.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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