Original Article

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 α 2 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: α 2 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 α 2 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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Access this article online

Quick Response Code:

Website: www.joacp.org

DOI: 10.4103/joacp.JOACP_235_18

How to cite this article: Silpa AR, Koshy KA, Subramanian A, Pradeep KK. 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. J Anaesthesiol Clin Pharmacol 2020;36:83-7.

Submitted: 03-Aug-2018 **Revised:** 27-Jan-2019 **Accepted:** 29-Mar-2019
Published: 18-Feb-2020

The primary objective of this study was to compare the efficacy of two different doses of dexmedetomidine (0.5 and 1μg/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 methyldopa, 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 received their cardiac medications 2 h before 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 (*n*=38)	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

	D1 (*n*=38)	D2 (*n*=38)
Hypertension	30	29
Diabetes mellitus	24	22
Old myocardial infarction	12	13
Beta-blockers	35	36
Calcium channel blockers	8	7
Angiotensin receptor blockers/ angiotensin converting enzyme inhibitors	9	8
Diuretics	3	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 (*n*=38)	Mean (standard deviation)	*P*
BIS at intubation	D1	50.1 (1.9)	0.206
	D2	49.5 (2)	
BIS 10 min after intubation	D1	48.9 (1.7)	0.170
	D2	48.3 (1.9)	
Sedation scoreat baseline	D1	1.7 (0.4)	1.000
	D2	1.7 (0.4)	
Sedation score after 5 min of drug infusion	D1	2.1 (0.4)	0.787
	D2	2.3 (0.4)	
Sedation score at the end of drug infusion	D1	3 (0.2)	0.562
	D2	3.1 (0.2)	

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

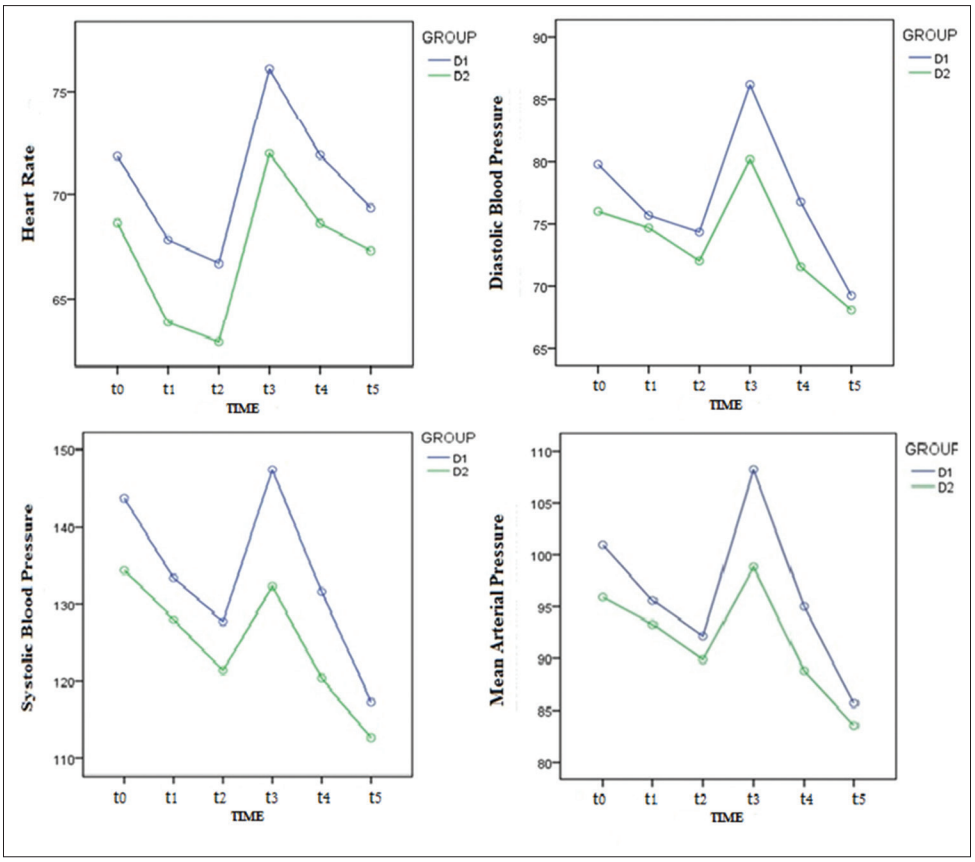

Figure 1: Mean plots for heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure. t0 = baseline before start of study drug infusion, t1 = 5 min after study drug infusion, t2 = pre intubation, t3 = 1 min after intubation, t4 = 3 min after intubation, t5 = 5 min after intubation

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.[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.[10] These properties make dexmedetomidine an ideal anesthetic adjuvant for coronary artery bypass grafting.

The hypotensive and negative chronotropic 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.[5,11] Similar results were obtained by Menda *et al.* [12]

Bradycardia was observed at the first and fifth minute after dexmedetomidine administration by Lawrence *et al*[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.[14] The initial hypertensive response is probably due to α 2 receptor stimulation of vascular smooth muscle. This response may be markedly decreased by slow infusion.[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.[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 dexmedetomidine1 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.*[16,17] Our results differ from those of Jarineshin *et al.*, who did not find any difference between the two doses.[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.[19]

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.

References

1. Loeb HS, Saudye A, Croke RP, Talano JV, Klodnycky ML, Gunnar RM. Effects of pharmacologically-induced hypertension on myocardial ischemia and coronary hemodynamics in patients with fixed coronary obstruction. Circulation 1978;57:41-6.
2. Hogue CW Jr, Talke P, Stein PK, Richardson C, Domitrovich PP, Sessler DI. Autonomic nervous system responses during sedative infusions of dexmedetomidine. Anesthesiology 2002;97:592-8.
3. Gerlach AT, Blais DM, Jones GM, Burcham PK, Stawicki SP, Cook CH, *et al*. Predictors of dexmedetomidine-associated hypotension in critically ill patients. Int J Crit Illn Inj Sci 2016;6:109-14.
4. Gerlach AT, Murphy CV. Dexmedetomidine-associated bradycardia progressing to pulseless electrical activity: Case report and review of the literature. Pharmacotherapy 2009;29:1492.
5. Sulaiman S, Karthekeyan RB, Vakamudi M, Sundar AS, Ravullapalli H, Gandham R. The effects of dexmedetomidine on attenuation of stress response to endotracheal intubation in patients undergoing elective off-pump coronary artery bypass grafting. Ann Card Anaesth 2012;15:39-43.
6. Naaz S, Ozair E. Dexmedetomidine in current anaesthesia practice- A review. J Clin Diagn Res 2014;8:GE01-4.
7. Pathak AS, Paranjpe JS, Kulkarni RH. Comparison of two doses of dexmedetomidine on haemodynamic stability in patients undergoing laparoscopic surgeries. JKIMSU 2016;5:35-43.
8. Keniya VM, Ladi S, Naphade R. Dexmedetomidine attenuates sympathoadrenal response to tracheal intubation and reduces perioperative anaesthetic requirement. Indian J Anaesth 2011;55:352-7.
9. Solanki N, Solanki R, Patel R, Garg A. Effect of dexmedetomidine to attenuate the sympathetic response of laryngoscopy and intubation and perioperative hemodynamic stability in patients undergoing neurosurgery. Indian J Heal Sci 2016;9:235-40.
10. Roekaerts PM, Prinzen FW, De Lange S. Beneficial effects of dexmedetomidine on ischaemic myocardium of anaesthetized dogs. Br J Anaesth 1996;77:427-9.
11. Sulhyan S, Vagarali A, Patil S, Dixit M. A comparative clinical study of dexmedetomidine versus placebo to attenuate hemodynamic response to endotracheal intubation in patients undergoing off pump coronary arterial bypass grafting. J Sci Soc 2014;41:151-5.
12. Menda F, Koner O, Sayin M, Ture H, Imer P, Aykac B. Dexmedetomidine as an adjunct to anesthetic induction to attenuate hemodynamic response to endotracheal intubation in patients undergoing fast-track CABG. Ann Card Anaesth 2010;13:16-21.
13. Lawrence CJ, De Lange S. Effects of a single pre-operative dexmedetomidine dose on isoflurane requirements and peri-operative haemodynamic stability. Anaesthesia 1997;52:736-44.
14. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology 1992;77:1134-42.
15. Stoelting RK. Circulatory changes during direct laryngoscopy and tracheal intubation: Influence of duration of laryngoscopy with or without prior lidocaine. Anesthesiology 1977;47:381-4.
16. Raval DL, Yadav VP. A comparative study of two different doses of dexmedetomidine on haemodynamic responses to induction of anaesthesia and tracheal intubation. J Clin Exp Res 2014;2:163-8.
17. Smitha KS, Shukla D, Sathesha M, Rao R, Nethra SS, Sudheesh K. Comparison of two different doses of dexmedetomidine in attenuating hemodynamic changes during laryngoscopy. J Evol Med Dent Sci 2014;3:13501-9.
18. Jarineshin H, Abdolahzade Baghaei A, Fekrat F, Kargar A, Abdi N, Navabipour S, *et al.* Comparison of two different doses of dexmedetomidine in attenuating cardiovascular responses during laryngoscopy and endotracheal intubation: A double blind, randomized, clinical trial study. J Med Life 2015;8:45-51.
19. Piao G, Wu J. Systematic assessment of dexmedetomidine as an anesthetic agent: A meta-analysis of randomized controlled trials. Arch Med Sci 2014;1:19-24.