Original Article

Effect of dexmedetomidine on attenuation of hemodynamic response to intubation, skin incision, and sternotomy in coronary artery bypass graft patients: A double-blind randomized control trial

Manoj Kamal, Deepa Agarwal, Geeta Singariya[1], Kamlesh Kumari, Bharat Paliwal, Shobha Ujwal[1]

Department of Anaesthesiology and Critical Care, All India Institute of Medical Sciences, [1]Department of Anaesthesiology and Critical Care, Dr S N Medical College, Jodhpur, Rajasthan, India

Abstract

Background and Aims: Coronary artery bypass grafting (CABG) surgery involves various noxious stimuli resulting in stress response, which in turn increases the risk of perioperative myocardial ischemia. The present study was conducted to evaluate the effect of dexmedetomidine on the attenuation of hemodynamic response to intubation, skin incision, and sternotomy in CABG surgery. **Material and Methods:** Sixty patients were randomized into two groups of 30 each. Group D patients received dexmedetomidine 1 µg/kg as loading dose over 10 min, followed by continuous infusion of 0.5 µg/kg/h. In group P, normal saline was infused as loading and maintenance dose at similar rate. Hemodynamic parameters, total induction dose of thiopentone, and adverse effects were recorded. Statistical analysis was performed using SPSS version 20.0. Chi-square test and ANNOVA test were used and $P < 0.05$ was considered significant. **Results:** The percentage increase in heart rate was significantly lesser in group D than group P after intubation (7.04% v/s 15.08%), skin incision (5.91% v/s 10.11%), and sternotomy (5.33% v/s 11.65%). Similarly increase in systolic, diastolic, and mean blood pressure were significantly lesser in group D than group P after intubation, skin incision, and sternotomy. There was a significant reduction of mean total of thiopentone in group D in comparison to group P. (1.16 mg/kg v/s 2.44 mg/kg) ($P<0.001$). **Conclusion:** Dexmedetomidine resulted in significant attenuation of hemodynamic response to intubation, skin incision, and sternotomy in CABG surgery without significant adverse effects. It also significantly reduced the dose of thiopentone required for induction.

Keywords: Dexmedetomidine, hemodynamic response, intubation, skin incision, sternotomy

Introduction

Coronary artery bypass graft (CABG) surgery involves various noxious and high-intensity surgical stimuli, resulting in stress response despite the adequate depth of anesthesia. The stimuli like laryngoscopy, tracheal intubation, skin incision, and sternotomy evokes a transient but marked sympathetic response, manifesting an increase in heart rate (HR) and blood pressure (BP). Although these responses may be of short duration and well tolerated by healthy individuals, serious complications may occur in patients with underlying coronary

Address for correspondence: Dr. Geeta Singariya,
123, Vaishali Avenue, Jhanwar Road, Jodhpur - 342 008,
Rajasthan, India.
E-mail: geetamanoj007@yahoo.co.in

artery disease or intracranial neurological pathology.[1] The postoperative myocardial injury has good correlation with changes in BP and HR during cardiac surgery.[2]

Various drugs such as lignocaine, opioids, nitroglycerine (NTG), calcium channel blockers (diltiazem) and β-blockers (esmolol) and techniques have been used till date to attenuate hemodynamic response, but none has been entirely successful.[3] Dexmedetomidine is a highly selective adrenoceptor agonist with a short half-life, which makes it an ideal drug for intravenous administration to blunt the pressure response.[4] Dexmedetomidine has anxiolytic, hypnotic, and analgesic properties and it is useful in the attenuation of the hemodynamic response to laryngoscopy and intubation, providing improved intraoperative hemodynamic stability and potentiating the effects of general anesthetic agents, thereby reducing their dose requirements for induction and maintenance of anesthesia[5,6] However, there is limited data available on attenuation of the hemodynamic response to skin incision and sternotomy in CABG. Hence, the present study was planned to evaluate the effect of intravenous dexmedetomidine on the attenuation of hemodynamic response resulting from laryngoscopy and tracheal intubation, skin incision, and sternotomy in CABG surgery. We hypothesized that dexmedetomidine attenuates the hemodynamic response resulting from intense noxious stimuli in CABG surgery. The primary objective was to compare hemodynamic variables and the secondary objectives were to compare the dose of thiopentone required for induction and to study any adverse effects related to dexmedetomidine.

Material and Methods

This study was conducted after approval from institutional ethics committee and clinical trial registry of India(CTRI/2018/07/014814). After obtaining written informed consent from patients, prospective, randomized, double-blind, and placebo-controlled study was carried from September2016toMarch2017. Total sixty patients of either sex, aged 40–75 years, belonging to ASA physical status II/III, scheduled to undergo elective off- pump CABG were enrolled from routine cardiac surgical operation list. The patients with anticipated or unanticipated difficult airway (laryngoscopy time lasting longer than 20 s), body mass index >30 kg/m², ejection fraction <40%, patients HR <50 beat/min, left main coronary artery occlusion >50%, preoperative valvular dysfunction, preoperative left bundle branch block, preoperative medication with clonidine or alpha-methyldopa, and severe lung, renal, or liver disease were excluded from the study.

Patients were randomly divided into group P (placebo,

$n = 30$) and group D (dexmedetomidine, $n = 30$) using computer-generated random number table, and the allocation was done using sequential number sealed opaque envelopes. The study drugs were prepared by an independent investigator who was not involved in recording the observations. The contents of the syringe were unknown to the anesthesiologist involved in administering the drug and recording of observations. Decoding was done on completion of the study.

The day before surgery, all patients were evaluated thoroughly in the pre anaesthetic clinic. Diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitor were stopped on the day before surgery but beta-blockers and statins were continued. All patients received oral alprazolam 0.25 mg and pantoprazole 40 mg night before the surgery and were kept fasted as per institutional guideline. On arrival to operation theatre, noninvasive monitoring in the form of electrocardiography, pulse oximetry, non-invasive blood pressure and bispectral (BIS) monitoring were applied and baseline (T1) vital parameters such as HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and arterial oxygen saturation (SpO_2), BIS score, and signal quality index (SQI) were recorded. A 18 G peripheral intravenous (i.v) cannula was secured and radial artery was cannulated with 20G cannula after local anesthetic infiltration with all aseptic precautions. Ringer lactate infusion was started at the rate 8–10 ml/kg/h After recording baseline vitals, study drug was administered using a syringe infusion pump as per the group allocation. Dexmedetomidine was diluted in saline to obtain a concentration of 0.1 μg/kg/mL, and patients received either the diluted dexmedetomidine or placebo saline at a rate of 60 ml/h for 10 min as loading dose (1 μg/kg) followed by maintenance dose (0.5 μg/kg/h) at a rate of 5 mL/h of same infusion till the 5 min after sternotomy. The study drugs were prepared in identical-looking syringes by independent investigator not involved in recording the observations. After infusion of the loading dose of study drug, anaesthesia was induced after preoxygenation with 100% oxygen with midazolam 0.05 mg/kg i.v, fentanyl 5 μg/kg i.v. followed by sodium thiopentone slow i.v. till BIS score achieved between 40-50. Vecuronium bromide 0.1 mg/kg i.v. administered to facilitate endotracheal intubation. After endotracheal intubation, right internal jugular vein cannulation was done by Seldinger technique under all aseptic precautions. Nasopharyngeal temperature, end-tidal carbon-di-oxide ($EtCO_2$), and urine output monitoring were done throughout the surgery. Anaesthesia was maintained with air oxygen mixture (50:50), vecuronium 0.02 mg/kg every 30 min and isoflurane to keep BIS score between 40-50. Intraoperative analgesia was supplemented with i.v fentanyl 1.0 μg/kg boluses, as judged by the increase in HR or SBP

by more than 20% of the baseline. Patients were ventilated to maintain $EtCO_2$ between 30-40 mmHg. HR, SBP, DBP, MBP, SpO_2, $EtCO_2$ BIS, and SQI were continuously monitored and recorded at baseline in preoperative period (T1), before starting infusion of study drug (T2), after administration of loading dose of study drug (T3), just before and after 1, 3, and 5 min of intubation (T4-7), skin incision (T8-T11), and sternotomy (T12-T15). Dexmedetomidine or placebo infusion was discontinued after 5 min of sternotomy and the rest of the anaesthetic management was carried out at the discretion of the attending anesthesiologist. The total dose of thiopentone required to achieve BIS score 40–50 was recorded. The side effects (bradycardia, tachycardia, hypotension, hypertension, and respiratory depression) of the study drugs, if any, were also recorded. In the event of bradycardia (HR <50 beats/min) with hypotension, 0.6 mg of atropine i.v was administered. The tachycardia (HR >20% of baseline) with BIS <50 was treated with fentanyl 1 μg/kg and if not normalized, then esmolol 5 mg incremental dose was given. Hypotension (SBP <20% of baseline mm Hg) was managed with 5 mg ephedrine i.v. In case of hypertension (SBP >20% of baseline) with tachycardia, fentanyl 1 μg/kg was given, and if not controlled than NTG 0.5 μg/kg/min was administered.

The calculated sample size of 27 patients in each group at 95% confidence interval 90% study power, to verify expected mean difference 10 beat/min change in HR from baseline to 1 min after intubation in both groups.[7] To cover for dropouts, we enhanced the estimated sample size, which was $n = 30$ in each group.

Power analysis was carried out by statistical software package SPSS version 20 (SPSS Inc., Chicago, IL, USA). The normalcy of data was checked by measures of skewness and Kolmogorov–Smirnov tests of normality. Demographic data were analyzed by Student's *t*-test and Chi-square test. ANOVA 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 tests with Bonferroni's correction. Intergroup comparisons for parameters were made with Students *t*-test. All data were expressed as mean ± SD (95% confidence intervals), and a P value < 0.05 was considered significant.

Results

The total 65 patients had met the criteria of eligibility and 60 patients were analyzed in the study. The demographic characteristics of the patients were comparable between both groups [Table 1].

Baseline hemodynamic parameters were comparable between the two groups. After the infusion of the loading dose of study drug, significant fall in HR was observed in group D as compared to the group P at all time points ($P < 0.01$) [Figure 1]. In group P, there was a statistically significant increase in HR at 1 and 3 min after intubation (15.08% and 9.65%), skin incision (10.11% and 6.73%), and sternotomy (11.65% and 9.3%) from the preintubation, preskin incision, and presternotomy values respectively, which normalised after 5 min. In group D, increase in HR was seen at 1 and 3 min after intubation (7.04% and 4.88%), skin incision (5.91% and 4.3%), and sternotomy (5.33% and 4.39%) from the preintubation, preskin incision, and presternotomy Values. The increase in HR was significantly less compared to the group P. The HR was lower at all time in group D compared to the baseline value [Figure 1].

On intergroup comparison of BP, it was observed that significantly lower SBP, DBP, and MAP were seen in group D compared to group P, at almost all time interval after infusion of study drug [Figure 2a-c]. In group P, there was a significant increase in SBP, DBP, and MBP after intubation, skin incision, and sternotomy when compared to both baseline as well as just before intubation, skin incision, and sternotomy values, typically seen after 1 min and 3 min, after which BP returned to near baseline values. In group D, although a slight rise in SBP, DBP, and MBP was observed after intubation, skin incision, and sternotomy when compared to just before intubation, skin incision, and sternotomy values, when compared to baseline, there was a statistically significant decrease in BP postintubation, postskin incision, and poststernotomy ($P < 0.001$). The group D had better control of HR and BP than group P.

The mean total dose of thiopentone for induction in group P was 139.2 ± 16.97 mg and in group D was 65.83 ± 12.25 mg, which comes out to be equivalent to 2.44 mg/kg in Group P and 1.16 mg/kg in Group D. The difference in mean dose of thiopentone between the two groups was statistically significant ($P < 0.001$) [Table 2].

Only one patient in group D had bradycardia, requiring treatment (atropine 0.6 mg), whereas no patient in group P

Table 1: Demographic characteristics of patients

	GROUP P (*n*=30)	GROUP D (*n*=30)	*P*
Age (years) (mean±SD)	59.23±6.99	59.93±7.03	0.700
Weight (kg) (mean±SD)	56.9±5.4	56.3±7.5	0.737
Sex (M/F) (numbers)	20/10	20/10	1.0
ASA (II/III) (numbers)	16/14	15/15	1.0

ASA: American Society of Anaesthesiologists Category

had bradycardia. Three patients in group D and one patient in group P had intraoperative hypotension required treatment (ephedrine 5 mg) ($P = 0.605$). Four patients in group D and 12 patients in group P had tachycardia, required esmolol treatment; this difference between the two groups was statistically significant ($P = 0.041$). One patient in group D and four patients in group P had hypertension, required NTG infusion ($P = 0.350$).

Discussion

In CABG patients, cardiovascular changes such as hypertension and tachycardia during tracheal intubation, or intense surgical stimuli like surgical incision and sternotomy are potentially detrimental and increases the risk of intraoperative myocardial ischemia and infarction.[1] The results of the present study illustrated that dexmedetomidine 1.0 µg/kg as an initial loading dose, followed by a continuous infusion of 0.5 µg/kg/h resulted in significant attenuation of cardiovascular responses to intubation, skin incision, and sternotomy in patients undergoing CABG surgery.

Dexmedetomidine is a highly specific and selective α 2 adrenoceptor agonist with hypnotic, sedative, anxiolytic, sympatholytic, and analgesic properties without producing respiratory depression. It also decreases intraoperative requirement of analgesics and anesthetics can also be used as an adjunct to general anesthesia.[4-6] Perioperative use of dexmedetomidine improves intraoperative haemodynamic stability resulting in decreased risk of adverse cardiac events, including myocardial ischemia.[8] Different doses of dexmedetomidine and the choice of the optimal dose of dexmedetomidine is very important to balance between the desired and side effects.[9] Administration of bolus dose of dexmedetomidine has biphasic response in blood pressure, initially transient increase of blood pressure and followed by
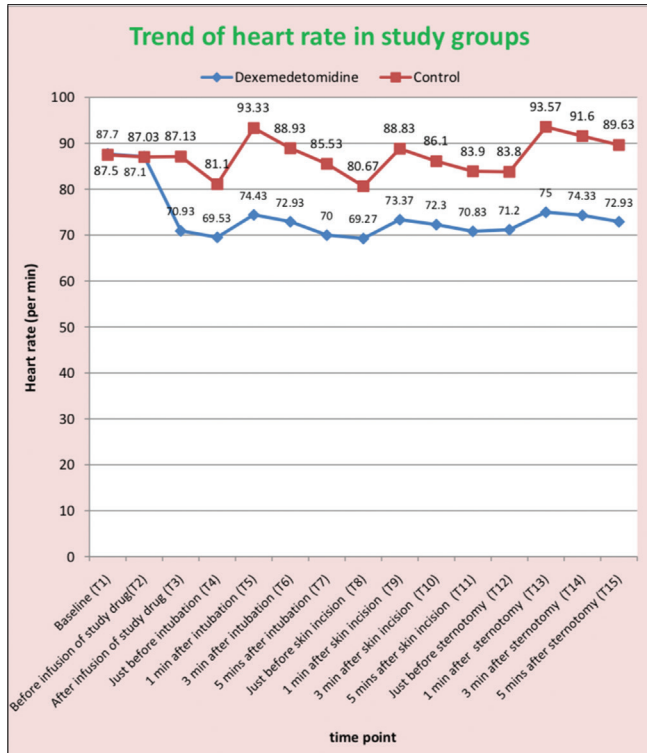

Figure 1: Trend of HR in the placebo and dexmedetomidine group

Table 2: Comparison of mean total dose of thiopentone

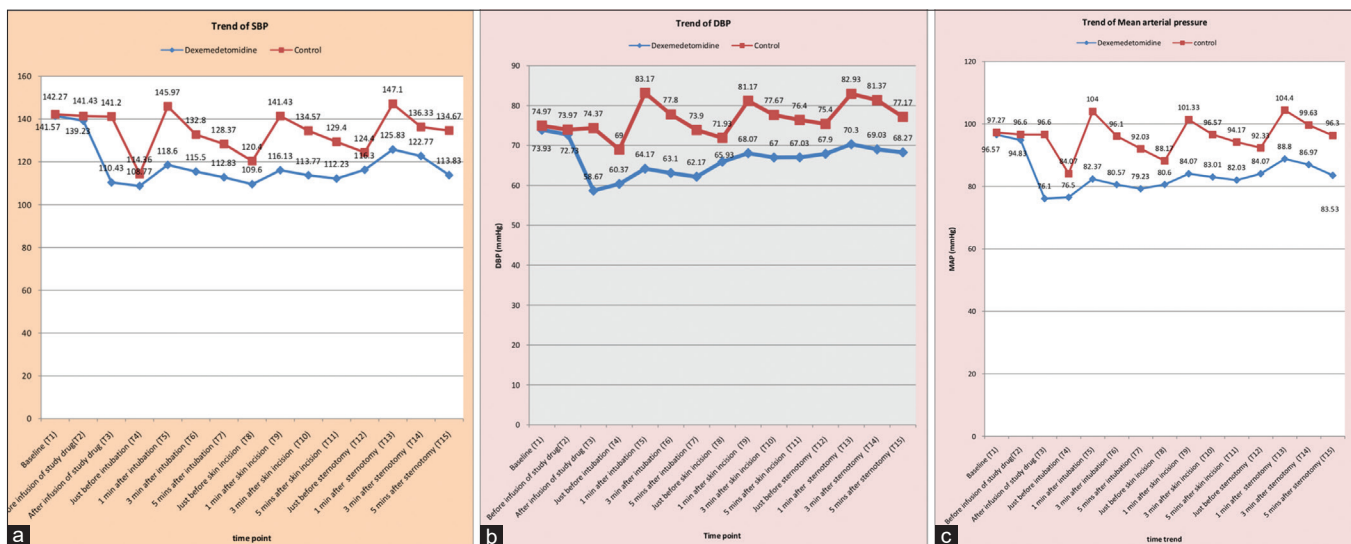| Thiopentone dose	GROUP P (n=30)	GROUP D (n=30)	P
Mean total dose	139.2±16.97	65.83±12.25	$P<0.001$
Mean dose (mg/kg)	2.44	1.16	$P<0.001$

Figure 2: (a) Trend of SBP in the placebo and dexmedetomidine group. (b) Trend of DBP in the placebo and dexmedetomidine group. (c) Trend of MAP in the placebo and dexmedetomidine group

hypotension. The hypertension is due to increase in systemic vascular resistance due to stimulation of peripheral α 2 receptors of vascular smooth muscles.[10] To abolish such initial hemodynamic response, we infused loading dose as continuous infusion over 10 min of time in our study.

In the present study, in group D, HR and MAP were significantly lower than group P at all time intervals, and the increase in HR and MAP after all types of intense noxious stimuli was significantly lower in group D as compared to group P, thereby showing that dexmedetomidine resulted in a significant attenuation of pressor response to endotracheal intubation and intense surgical stimuli. Our results are in agreement with the previous studies by Yildiz *et al.*,[10] Menda *et al.*,[11] Bajwa *et al.*,[12] and Laha *et al.*[13] who have reported similar attenuation of the pressor response to laryngoscopy and intubation by using dexmedetomidine in a dose of 1 μg/kg and concluded that dexmedetomidine can safely be used to attenuate the hemodynamic response to endotracheal intubation. Sulaiman *et al.*[7] also observed similar results with single low dose of dexmedetomidine (0.5 μg/kg slow i.v. infusion in 10 min, 15 min prior to TI) in patients undergoing off-pump CABG. Similar results were seen by Basar *et al.*[14] and Kumari *et al.*[15] with smaller dose of dexmedetomidine (0.5–0.6 μg/kg i.v.) in non cardiac surgeries.

Our results were in agreement with Mukhtar *et al.*[16], Totonchi *et al.*[17] and Klamt *et al.*[18] They observed that the rise in HR and MAP after skin incision and sternotomy were less in dexmedetomidine group compared to the control group in pediatric and adult patients undergoing cardiac surgery.

Efe *et al.*[19] compared between bolus of esmolol, infusion of esmolol and control and found esmolol infusion was more effective than esmolol bolus on controlling HR and BP during both intubation and sternotomy. Marashi *et al.*[20] studied the effect of magnesium sulfate bolus and infusion on haemodynamic changes during sternotomy and found increased HR in study group and control group but this increment was significantly lesser in the study group.

In our study, we used thiopentone as slow i.v bolus for induction though the choice of induction agents for CABG surgery is always debatable. The use of propofol and etomidate has been considered superior to other intravenous anesthetic agents in cardiac patients but cost disadvantage is always a concern, especially in developing countries. Singh *et al.*[21] compared the hemodynamic effects of anesthesia induction with etomidate, thiopentone, propofol, and midazolam in patients with coronary artery disease and left ventricular dysfunction and found that all the four anesthetic agents were acceptable for induction. They concluded that the hemodynamic effects of anesthetic induction agents in cardiac patients depend to a great extent, on the technique, skill, and experience of drug administration by the clinician (e.g., slow infusion v/s rapid bolus). Dose adjustment and speed of induction are probably more important than which individual drugs are used. In the present study to prevent hypotension during induction, we preferred thiopentone over propofol for induction.

The dexmedetomidine also has sedative and anesthetic sparing effect.[5,6,22,23] In the present study, significant reduction in induction dose of thiopentone (52.8% lesser in dexmedetomidine group) was seen in dexmedetomidine group (1.16 mg/kg) compared to placebo group (2.44 mg/kg). Our results are in agreement with the previous studies which reported significant reduction in the induction dose of thiopentone with the use of dexmedetomidine.[6,10,14]

Dexmedetomidine as a continuous infusion was well tolerated in cardiac patients and no serious adverse effects were seen.[7,11,16,17] Bradycardia was observed in only one patient and intraoperative hypotension in three patients in the dexmedetomidine group, which required pharmacological intervention. None of the patients in either group had respiratory depression, indicating the safety profile of using dexmedetomidine as a continuous infusion in cardiac patients.

There are a few limitations in our study. Cardiac index and pulmonary capillary wedge pressure, which are a better guide for cardiac performance, were not used in the present study. In addition, the measurement of QT interval and plasma catecholamine levels was not done in the present study which are more objective means of evaluating stress and hemodynamic response.

Conclusion

We conclude that initial loading dose of dexmedetomidine 1.0 μg/kg given over a period of 10 min before the induction of anaesthesia, followed by a continuous infusion of dexmedetomidine 0.5 μg/kg/h till the 5 min after sternotomy, significantly attenuated the hemodynamic responses associated with laryngoscopy and intubation, skin incision, and sternotomy. It also reduced the dose of thiopentone required for induction and was not associated with any significant adverse effects.

Conflicts of interest

There are no conflicts of interest.

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