Original Article

Impact of Dexmedetomidine on Hemodynamic Changes during and after Coronary Artery Bypass Grafting

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Abstract

Objective: To determine the effect of dexmedetomidine (Dex) on hemodynamic changes during cardiopulmonary pump and postoperative period in coronary artery bypass grafting (CABG). **Methods and Design:** This study is designed as a double-blinded, randomized clinical trial. **Setting:** University hospital and single center. **Participants:** patients candidate for elective CABG. **Intervention:** Dex 0.5 µg/kg/h or placebo was infused from the initiation of anesthesia up to extubation in Intensive Care Unit (ICU). **Measurements:** Heart rate (HR) and blood pressure (BP), pain score, and total morphine dose requirement were monitored and compared during cardiac pump up to 12 h postoperative in ICU. **Results:** Mean arterial pressure was significantly higher in Dex group in postoperation period at 1 ($P = 0.010$) and 2 h ($P = 0.002$) compared to control group. HR was significantly lower in Dex group in postcardiopulmonary bypass (CPB) time at 0 h ($P = 0.001$), 1 h ($P = 0.0016$), and 2 h ($P = 0.001$), and then in postoperative period in ICU at 1 h ($P = 0.025$), 2 h ($P = 0.0012$), and 4 h ($P = 0.0025$) compared to control group. Postoperative pain score was significantly lower during 12 h after surgery. **Conclusion:** Dex could effectively blunt hemodynamic response to surgical stress, particularly during CPB pump and afterward. Infusion of Dex maintains BP at higher range and HR at lower range compared to placebo.

Keywords: *Coronary artery bypass grafting, coronary, dexmedetomidine, hemodynamic*

Introduction

Dexmedetomidine (Dex), a highly selective α2-adrenergic receptor agonist,[1] is a newly discovered drug gained much reputation in neuroanesthesia, Intensive Care Unit (ICU), and cardiac anesthesia in recent years.[2] Dex shows a high ratio of specificity for the α2 receptor (α2/α1 1600:1) compared with clonidine (α2/α1 200:1), making it a complete α2 agonist.[3] Compared to clonidine, Dex has proposed unique features to maintain analgesia, anxiolytic, and sedative effect without causing major respiratory depression in this sense. It has been used to facilitate weaning from mechanical ventilation and to sedate patients with noninvasive ventilation.[4,5]

Dex, by activation of α2-adrenergic receptor, produces sedation which mimics natural Stage 2 nonrapid eye movement sleep and helps in early postoperative recovery.[6] Activation of α2 receptors induces a central inhibition of sympathetic stimulation that results hypotension and bradycardia along with decreased need for opioids and more stable hemodynamics in early postoperative recovery.[7-10] Dex is less respiratory depressant and allows safer recovery.[11,12]

Recent researches have shown that Dex could be used as an adjunct to general anesthesia instead of main hypnotic drug for induction.[13] Dex decreases the anesthetic and opioid requirements in surgical procedures to blunt sympathetic-mediated hyperdynamic response to surgical stress.[14] Here, in this study, we embarked on the effect of infusion of Dex on stabilization of hemodynamic changes during cardiopulmonary pump in coronary artery bypass grafting (CABG).

Objective

To determine the effect of Dex on hemodynamic changes during cardiopulmonary pump and postoperative period in CABG.

Methods

Ethics

The study was reviewed and approved by the Shahid Beheshti University of

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Medical Sciences Ethics Committee and been performed in accordance. Information about the study was given comprehensively both orally and in written form to all patients or their accompanying adult. They gave their informed written consents before their inclusion in the study.

Study design

The study was designed as a double-blinded, randomized clinical trial. Randomization was performed based on accidental numbers assigned to each patient by computer.

The study was double blind as evaluating anesthesiologist was blinded to the group of the patient. Patients were also blinded to the drug that was administered. Drugs were also delivered in the same size syringe and same color to the anesthesiologist performing spinal anesthesia (concealment allocation).

Patient selection

In a randomized clinical trial, 88 patients candidate for elective CABG enrolled and randomly assigned to Dex and control group. The study was performed in a 10-month period from 2014 to 2015. Inclusion criteria were patients with American Society of Anesthesiologists Class I, II, and III with no history of high-grade heart failure, no sever uncontrolled hypertension (HTN) or hypotension, no pacemaker or intracardiac devices and no bradycardia or arrhythmia.

Exclusion criteria were patients with bleeding >1000 ml during or after surgery, patients with >4 grafts, duration of cardiopulmonary bypass (CPB) >2 h, intubation time >2 h, heparin resistance during CPB pump. The rational for that is the blunted response of patients with heart failure to hemodynamic changes, the higher chance of arrhythmia in patients with >4 grafts, and increased hemodynamic instability in patients with CPB time >2 h. It is corrected in revised manuscript.

Dexmedetomidine infusion

Dex 0.5 μg/kg/h was infused from the initiation of anesthesia up to extubation in ICU. In placebo group, patients received the same volume of 0.9% saline. Infusion of Dex continued and the patient was transferred to ICU. Eight dropouts occurred due to these postinitiation exclusion criteria.

Monitoring

Patients were admitted to operating room and were monitored for pulse oximetry, arterial line and invasive blood pressure (BP) monitoring, electrocardiogram, capnography, and bispectral index for depth of anesthesia. Hemodynamic parameters (systolic arterial pressure [SAP], heart rate [HR] and peripheral oxygen saturation) were recorded by an anesthetist who was blinded to the patient group, in post-CPB time at 0, 1, and 2 h, and then in postoperative period in ICU at 1, 2, 4, 6, and 12 h.

Anesthesia

General anesthesia was induced and maintained by the same method. After establishing full cardiovascular monitoring, general anesthesia was induced with fentanyl 2 μg/kg, midazolam 0.05 mg/kg, lidocaine, and etomidate 1–2 mg/kg until loss of eyelid reflex. Orotracheal intubation was facilitated by 0.1 mg/kg cisatracurium. Routine airway and ventilator management were used as appropriate for the type of surgery. Anesthesia was maintained with oxygen and isoflurane (1%–1.2% end-tidal concentration) and continuous infusion of fentanyl 50 μg/h until patient transfer to open-heart ICU. Neuromuscular relaxation was maintained by continuous infusion of cisatracurium 1–2 μg/kg/min required to maintain 90%–95% twitch inhibition under inhalational anesthesia. After surgery, patients were not reversed for muscle relaxation.

Infusion of Dex was started at CPB time and then after CPB and continued when the patient was transferred to ICU. Patients were not extubated until completely awake and no sign of arrhythmias and bleeding. Target range for hemodynamic drop was if systolic BP (SBP) <90 mmHg then infusion of epinephrine 2–10 μg/min was maintained.

Measuring hemodynamics and pain score

In all patients, baseline SAP, diastolic arterial pressure, mean arterial pressure (MAP), and baseline HR values were recorded after a 3 min resting period following the insertion of the radial artery catheter.

Hemodynamic parameters including MAP and HR were recorded by an anesthetist who was blinded to the patient group, at baseline after induction of anesthesia and every 10 min thereafter. For comparing changes of hemodynamics during CPB and postoperation, MAP and HR were recorded in post-CPB time at 0, 1, and 2 h, and then in postoperative period in ICU at 1, 2, 4, 6, and 12 h.

Pain score was measured using a 10-point scoring system of numerical rating scale (NRS) in 12 h postoperative period. Total dose of morphine requirement was also measured during 24 h postoperative period.

Statistical analysis

All data are presented as mean ± standard deviation. Demographic data were analyzed by Student's *t*-test or Mann–Whitney U-test. Analysis of variance for repeated measures was used to analyze hemodynamic changes over time between two groups.

Sample size

Sample size was estimated using sample size calculator software with 95% confidence interval (CI), P = 0.05 and power of 80% and mean and variance of 75 and 12 in group experiment and mean and variance of 70 and 9 in group control in primary outcome (MAP) based on pilot study.

Results

Total numbers of eighty patients were enrolled in this study and were randomly assigned to one of Dex or control groups of study. The age, sex, and body mass index were not significantly different between two groups of study ($P > 0.05$) [Table 1]. Duration of CPB and surgery were not also significantly different between two groups of study ($P > 0.05$) [Table 1].

The frequency of coronary artery disease based on vessels involvement and ejection fraction and history of chronic disease including HTN, cerebrovascular disease, diabetes mellitus, and peripheral vascular disease in patients of the study was not significantly different in two groups of study ($P > 0.05$) [Table 2].

Hemodynamic

Hemodynamic variables including HR and MAP were compared between two groups of study. MAP was not significantly different between two groups of study at the baseline of start of CPB pump ($P > 0.05$). MAP was significantly higher in Dex group in postoperation period at 1 ($P = 0.010$) and 2 h ($P = 0.002$) compared to control group [Figure 1].

HR was significantly lower in Dex group in post-CPB time at 0 h ($P = 0.001$), 1 h ($P = 0.0016$), and 2 h ($P = 0.001$), and then in postoperative period in ICU at 1 h ($P = 0.025$), 2 h ($P = 0.0012$), and 4 h ($P = 0.0025$) compared to control group [Figure 2].

Table 1: Demographic variables in patients in Dexmedetomidine group and control group

Variable	Dexmedetomidine (*n*=40)	Control (*n*=40)	*P*
Age	49.9±11.2	51.5±12.6	0.33
Sex (male/female)	39/11	42/8	0.21
BMI	25.5±5.2	25.8±5.6	0.37
Duration of CPB	65.7±21.7	63.4±22.8	0.20
Duration of Surgery	5.13±1.76	5.40±1.9	0.26

Table 2: Variables of coronary artery disease and ejection fraction and history of diseases

Variable	Dexmedetomidine (*n*=40)	Control (*n*=40)	*P*
Number of CAD			
LAD	16	12	0.067
2 vessels	18	20	
3 vessels	16	18	
Ejection Fraction	46.3±7.3	47.5±6.9	0.28
History of chronic disease			
HTN	7	8	0.31
CVA	4	3	
DM	9	11	
PVD	5	5	

HTN: hypertension; CVA: Cerebro vascular accident; DM: Diabetes mellitus; PVD: peripheral vascular disease

Percentage of patients on epinephrine was not significantly different in Dex group (30%) and control group (42.5%). Amount of fluid administered during operation, postoperative hemoglobin, and use of beta-blockers at the time of transfer to ICU are presented in Table 3.

Linear mixed model showed that there is a statistically significant difference between the groups regarding the mean SBP, diastolic BP (DBP), and HR after adjustment for the baseline values ($P < 0.05$). In addition, after considering the multiple comparison by Bonferroni method, we found that the difference in SBP between control and Dex was significant (difference = 3.1, 95% CI: 1.3–8.5, $P = 0.012$). Furthermore, the difference in DBP between control and Dex group was significant (difference = 3.2, 95% CI: 1.1–7.2, $P = 0.0017$). We found that the difference in HR between control and Dex group was significant (difference = 2.2, 95% CI: 1.6–3.8, $P = 0.022$).

Postoperation pain

Postoperation pain score was compared between Dex group and control group. In Dex group, postoperative pain score measured by NRS score was significantly lower at 2 ($P = 0.01$), 4 ($P = 0.014$), 6 ($P = 0.025$), 8 ($P = 0.005$), 10 ($P = 0.018$), and 12 ($P = 0.001$) h compared to control group [Figure 3].

Postoperative morphine requirement

Postoperative morphine requirement was compared between two groups of study. Morphine requirement was significantly lower in Dex group at 4, 12, and 24 h postoperation compared to control group [Table 4].

Discussion

Our results showed that Dex stabilizes BP and HR during CPB pump and in postoperative period in ICU. Dex has a binary effect: on one side decrease BP response to surgical stress and on the other side minimize surge in BP and HR postCPB and postoperative ICU. The use of α2-agonists aims at blunting the hemodynamic stress response. Therefore, one would expect an increased BP and HR with placebo which is blunted by the administration of Dex.

Dex infusion before start of CPB can suppress the increase in BP and blunt the cardiovascular responses to CPB stress.[15] Effect of CPB pump is not different from surgical stress in which instability is the major feature. Much has been written about the rapid and profound inflammatory response that CPB elicits.[16] CPB initiates cascades of inflammatory cytokines that could induce vasodilation. Previous studies have demonstrated that Dex has anti-inflammatory property.[17]

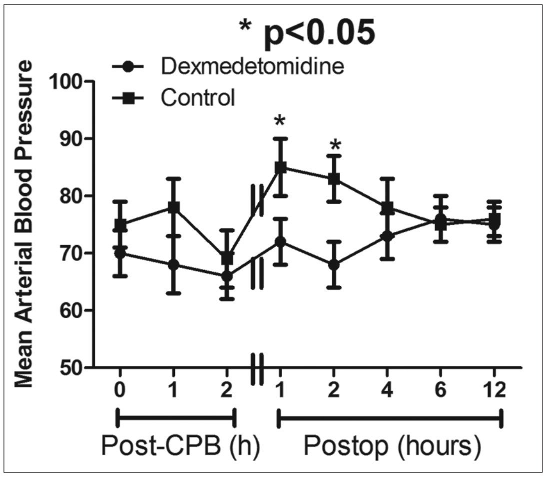

Figure 1: Mean arterial blood pressure during cardiopulmonary bypass pump and postoperative period in open-heart Intensive Care Unit

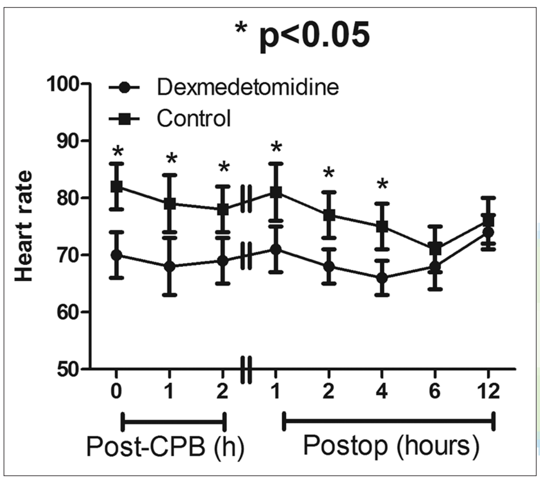

Figure 2: Heart rate after cardiopulmonary bypass pump (postcardiopulmonary bypass time) and postoperative period in open-heart Intensive Care Unit (postoperative)

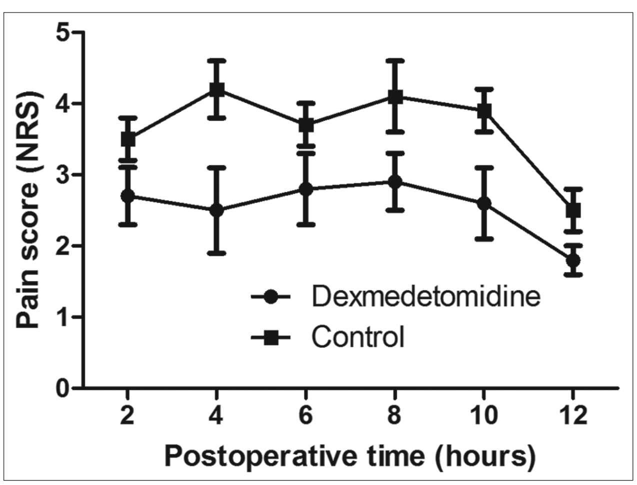

Figure 3: Postoperation pain score in dexmedetomidine and control group

It has been demonstrated that Dex combined with fentanyl stabilizes hemodynamics and suppresses the decrease in BP during anesthetic induction in patients undergoing cardiac surgery.[18] Besides, Dex can safely be used to attenuate the hemodynamic response to endotracheal intubation in patients undergoing CABG.[19] Previous studies have shown that Dex can stabilize BP and HR; however, the occurrence of bradycardia and hypotension in the Dex group was also higher than the control group.[20]

Table 3: Percent of patients received epinephrine and beta-blocker at the time of transfer to ICU

Variable	Dexmedetomidine (n=40)	Control (n=40)	P
Epinephrine administered (%)	12 (30%)	16 (42.5%)	0.34
Fluid administered	2667±1205	2852±1329	0.51
Post-operative Hb	10.1±2.4	10.6±2.8	0.39
Beta-blocker administered (%)	5 (12.5%)	9 (22.5%)	0.23

Table 4: Post-operative morphine requirement in two groups of study

Morphine requirement (mg)	Dexmedetomidine (n=40)	Control (n=40)	P
4 hours	4.2±0.8	5.2±0.9	0.001
12 hours	6.9±1.1	7.7±1.2	0.002
24 hours	8.6±1.3	9.5±1.1	0.001

Infusion of Dex without bolus seems to be an effective adjuvant to fentanyl on the control of hemodynamic responses during pediatrics cardiac surgery.[21] We showed that infusion of Dex without fentanyl stabilizes hemodynamics during CPB pump and postoperative. It is important to note that in our study, Dex was infused at lower dose 0.5 µg/kg/h compared to 1 µg/kg/h in Klamt study.[22] Our results depicted that, due to its short half-life and high elimination rate, Dex infusion at low dose of 0.5 µg/kg/h should be continued without delaying awakening of patients in postopen-heart ICU.

BP was stabilized in Dex group compared to control group (minimize both surge and drop in BP). Although the real mechanism behind this is still unknown, several explanations have been suggested. The first mechanism is that using Dex as adjuvant could decrease hemodynamic response and the total dose of required hypnotic, less intraoperative opioid consumption.[23] Dex has been used as total intravenous anesthesia at doses as high as 10 µg/kg/h without inducing hypotension or severe bradycardia.[24] In fact, Dex improves cardiovascular hemodynamics by decreasing dose of hypnotic for maintenance of anesthesia and its cardio depressant and vasodilator effect. Besides, Dex infusion may decrease the dose needed for Midazolam and fentanyl combination which depress the HR, BP, and cardiac index.[25]

Sympathetic overstimulation could induce unsteadiness in BP and HR during CPB pump. Dex could centrally block α2 receptor and decrease excitation of sympathetic neurons activity. This central inhibition of sympathetic system could minimize patient stress and instability in BP during and after CPB and in ICU. In addition, this central inhibition of sympathetic system could prevent sympathetic reservoir to be depleted and therefore Dex group have higher BP compared to control group. Mukhtar *et al*. used a dosage similar to our study for normal adult patients (0.5 μg/kg/h infusion) which was effective to attenuate the hemodynamic and neuroendocrine response to surgery, without any hemodynamic deleterious effect.[26] The loading dose of Dex but not infusion may be followed by severe hypotension, bradycardia, or sinus arrest, especially during rapid loading, in young patients.[27]

Infusion of Dex decreased the postoperative pain and morphine requirement in our patients. The importance of preemptive analgesia has been emphasized in recent publications. Dex is effective drug in providing preemptive analgesia by decreasing central and peripheral sensitization through effect on locus cereleus.[28]

Conclusion

Dex could effectively blunt hemodynamic response to surgical stress particularly during CPB pump and afterward. Infusion of Dex maintains BP and HR at higher range than placebo.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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