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

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 h ($P = 0.010$) 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 Medical Sciences, Tehran, Iran.

How to cite this article: Hashemian M, Ahmadinejad M, Mohajerani SA, Mirkheshti A. Impact of dexmedetomidine on hemodynamic changes during and after coronary artery bypass grafting. Ann Card Anaesth 2017;20:152-7.

Morteza Hashemian, Mehdi Ahmadinejad, Seyed Amir Mohajerani, Alireza Mirkheshti

Department of Anesthesiology and Pain Medicine, Kerman University of Medical Sciences, Kerman, 1Department of Anesthesiology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Address for correspondence:
Dr. Alireza Mirkheshti,
Department of Anesthesiology, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail: drmirkheshti@gmail.com

Access this article online
Website: www.annals.in
DOI: 10.4103/aca.ACA_76_16
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 µg/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 1].

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].

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 $\alpha$2-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]
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.\[20\] Infusion of Dex without bolus seems to be an effective adjuvant to fentanyl on the control of hemodynamic responses during pediatric 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.\[25\]

| 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|

| 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|
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. 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.

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.

**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.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Kamibayashi T, Maze M. Clinical uses of alpha2 -adrenergic agonists. Anesthesiology 2000;93:1345-9.
2. Ishikawa S, Kugawa S, Neya K, Suzuki Y, Kawasaki A, Hayama T, et al. Hemodynamic effects of dexmedetomidine in patients after cardiac surgery. Minerva Chir 2006;61:215-9.
3. Menda F, Kőner O, Sayın M, Türe H, İmer P, Ayaç 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.
4. Akada S, Takeda S, Yoshida Y, Nakazato K, Mori M, Hongo T, et al. The efficacy of dexmedetomidine in patients with noninvasive ventilation: A preliminary study. Anesth Analg 2008;107:167-70.
5. Takasaki Y, Kido T, Semba K. Dexmedetomidine facilitates induction of noninvasive positive pressure ventilation for acute respiratory failure in patients with severe asthma. J Anesth 2009;23:147-50.
6. Akin A, Bayram A, Esmaoglu A, Tosun Z, Aksu R, Altuntas R, et al. Dexmedetomidine vs. midazolam for premedication of pediatric patients undergoing anesthesia. Paediatr Anaesth 2012;22:871-6.
7. Arora D, Mehta Y. Recent trends on hemodynamic monitoring in cardiac surgery. Ann Card Anaesth 2016;19:580-3.
8. Everett LL, van Rooyen IF, Warner MH, Shurtleff HA, Saneto RP, Ojemann JG. Use of dexmedetomidine in awake craniotomy in adolescents: Report of two cases. Paediatr Anaesth 2006;16:338-42.
9. Xu M, Kontinen VK, Kalso E. Effects of radolmidine, a novel alpha2-adrenergic agonist compared with dexmedetomidine in different pain models in the rat. Anesthesiology 2000;93:473-81.
10. Kundra TS, Nagaraja PS, Singh NG, Dhananjaya M, Sathish N, Manjunatha N. Effect of dexmedetomidine on diseased coronary vessel diameter and myocardial protection in percutaneous coronary intervention patients. Ann Card Anaesth 2016;19:394-8.
11. Ren J, Zhang H, Huang L, Liu Y, Liu F, Dong Z. Protective effect of dexmedetomidine in coronary artery bypass grafting surgery. Exp Ther Med 2013;6:497-502.
12. Cetin M, Birbicier H, Hallioglu O, Orekeçi G. Comparative study between the effects of dexmedetomidine and propofol on cerebral oxygenation during sedation at pediatric cardiac catheterization. Ann Card Anaesth 2016;19:20-4.
13. McCutcheon CA, Orme RM, Scott DA, Davies MJ, McGlade DP. Comparison of dexmedetomidine versus conventional therapy for sedation and hemodynamic control during carotid endarterectomy performed under regional anesthesia. Anesth Analg 2006;102:668-75.
14. Gerlach AT, Dasta JF. Dexmedetomidine: An updated review. Ann Pharmacother 2007;41:245-52.
15. Kunitsa T, Ueno M, Kurosawa A, Nagashima M, Hayashi D, Sasakawa T, et al. Dexmedetomidine can stabilize hemodynamics and spare anesthetics before cardiopulmonary bypass. J Anesth 2011;25:818-22.
16. Gal J, Smith A, Riedel B, Ryston D. Preservation and protection of myocardial function. J Cardiothorac Vasc Anesth 2000;14:3 Suppl 1:22-36.
17. Xu Y, Zhang R, Li C, Yin X, Lv C, Wang Y, et al. Dexmedetomidine attenuates acute lung injury induced by lipopolysaccharide in mouse through inhibition of MAPK pathway. Fundam Clin Pharmacol 2015;29:462-71.
18. Kunitsa T, Nagata O, Nagashima M, Mitamura S, Ueno M, Suzuki A, et al. Dexmedetomidine suppresses the decrease in blood pressure during anesthetic induction and blunts the cardiovascular response to tracheal intubation. J Clin Anesth 2009;21:194-9.
19. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. Br J Anaesth 2002;88:669-75.
20. Piao G, Wu J. Systematic assessment of dexmedetomidine as an anesthetic agent: A meta-analysis of randomized controlled trials. Arch Med Sci 2014;10:19-24.
21. Klamt JG, Vicente WV, Garcia LV, Ferreira CA. Hemodynamic effects of the combination of dexmedetomidine-fentanyl versus midazolam-fentanyl in children undergoing cardiac surgery with cardiopulmonary bypass. Rev Bras Anestesiol 2010;60:350-62.
22. Klamt JG, de Andrade Vicente WV, Garcia LV, Ferreira CA.
Effects of dexmedetomidine-fentanyl infusion on blood pressure and heart rate during cardiac surgery in children. Anesthesiol Res Pract 2010;2010. pii: 869049.

23. Peng K, Wu S, Liu H, Ji F. Dexmedetomidine as an anesthetic adjuvant for intracranial procedures: Meta-analysis of randomized controlled trials. J Clin Neurosci 2014;21:1951-8.

24. Shukry M, Kennedy K. Dexmedetomidine as a total intravenous anesthetic in infants. Paediatr Anaesth 2007;17:581-3.

25. Rivenes SM, Lewin MB, Stayer SA, Bent ST, Schoenig HM, McKenzie ED, et al. Cardiovascular effects of sevoflurane, isoflurane, halothane, and fentanyl-midazolam in children with congenital heart disease: An echocardiographic study of myocardial contractility and hemodynamics. Anesthesiology 2001;94:223-9.

26. Mukhtar AM, Obayah EM, Hassona AM. The use of dexmedetomidine in pediatric cardiac surgery. Anest Analg 2006;103:52-6.

27. Deutsch E, Tobias JD. Hemodynamic and respiratory changes following dexmedetomidine administration during general anesthesia: Sevoflurane vs. desflurane. Paediatr Anaesth 2007;17:438-44.

28. Miller RD, Eriksson LI, Fleisher L, Wiener-Kronish JP, Young WL. Miller's Anesthesia. 8th ed. Philadelphia: Churchill Livingstone, Elsevier; 2015.