Original Article

Effects of Dexmedetomidine on Endogenous Antioxidant Levels and Clinical Outcomes Among Patients Undergoing Coronary Artery Bypass Grafting: A Randomized Clinical Trial

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ABSTRACT

Background: Dexmedetomidine reduces perioperative catecholamine concentrations and confers hemodynamic and sympathetic stability. It adjusts coronary blood flow and is known as one of the ideal anesthetic drugs, especially for patients undergoing coronary artery bypass graft surgery (CABG). The present study was performed to evaluate the potential of dexmedetomidine to protect against oxidative stress during CABG.

Methods: The present double-blinded randomized clinical trial was performed on 58 patients undergoing CABG at Rajaie Cardiovascular Medical and Research Center. After anesthesia induction, the patients were allocated to the trial (dexmedetomidine) and control (normal saline solution) groups. Total antioxidant capacity and malondialdehyde were measured in samples obtained from arterial catheters before the intervention, after pump weaning, and 24 hours after intensive care unit (ICU) admission.

Results: Only total antioxidant capacity and malondialdehyde at the third measurement point at the ICU were lower in the trial group than in the control group. The levels of circulatory antioxidants were higher in the trial group than in the control group before the intervention and after pump weaning. No significant differences were observed regarding circulatory antioxidant levels between the trial and control groups.

Conclusions: Dexmedetomidine infusion before and during CABG might improve endocardial blood flow and hemodynamic stability among patients undergoing CABG. ***(Iranian Heart Journal 2023; 24(3): 24-31)***

KEYWORDS: Oxidative stress, CABG, Dexmedetomidine, Cardiopulmonary bypass

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Endotoxemia and ischemia occur during coronary artery bypass graft surgery (CABG), leading to an inflammatory response [1-4] due to lipopolysaccharide release from the cell walls of Gram-negative bacteria. Proinflammatory cytokines and nitric oxides are released by elevated endotoxins levels and patients' oxygen usage. [5,6] Dexmedetomidine has sedative and analgesic impacts, and its anxiolytic and dose-related sedative impacts are comparable with GABAergic drugs, such as midazolam and propofol. [7,8] Dexmedetomidine reduces preoperative catecholamine concentrations and confers preoperative hemodynamic and sympathetic stability. [9, 10] Several studies have shown that dexmedetomidine can diminish cardiovascular complications, including myocardial ischemia. Dexmedetomidine adjusts coronary blood flow and, accordingly, is an ideal anesthetic drug, especially for patients undergoing CABG. [7,11] For instance, laryngoscopy and endotracheal intubation after anesthesia are associated with hemodynamic changes and the stimulation of sympathetic system reflexes, causing hypertension, tachycardia, and arrhythmia. [12,13] Preoperative dexmedetomidine usage can modulate stress response factors and inflammatory factors in the circulation of patients and increase the hemodynamic stability of patients undergoing CABG. [14-16] Moreover, animal studies have shown that dexmedetomidine can prevent sepsis-related renal and pulmonary impairments by decreasing inflammatory cell migration. Ammar et al [17] reported that dexmedetomidine had cardiac and renal protective roles among patients undergoing CABG by lessening myocardial-specific and renal-specific proteins and prolapsing inflammatory cytokines. Consequently, dexmedetomidine is a potent inhibitor of surgical stress response and can reduce oxidative stress in CABG.

The present study was performed to evaluate the impact of dexmedetomidine on circulatory antioxidant levels and clinical outcomes in patients undergoing CABG.

METHODS

Trial Design

The present double-blinded randomized clinical trial was performed with a parallel design on 58 patients undergoing CABG at Rajaie Cardiovascular Medical and Research Center between control and dexmedetomidine groups. The study protocol was approved by the Research Ethics Committee of Iran University of Medical Sciences and registered on the IRCT website (IRCT20170912036157N1). Before the trial commencement, the study participants signed informed consent.

Sample Size and Randomization Sequences

According to the Cochran sample size formula, the calculated sample size was 80 patients. The study samples were randomly selected from all adult patients who met the eligibility criteria. Eighty participants were randomly selected from adult patients referred to the hospital for CABG. Among the included patients, 22 participants were excluded due to a history of CABG (n=10), deep hypothermia (n=2), low ejection fractions (n=3), untouchable peripheral pulses (n=4), and dexmedetomidine sensitivity or its usage during the previous week (n=3). The study participants were randomly allocated via the block randomization method to trial and control groups. Patients in both groups and surgeons were blinded to the randomization and the study groups. No patients in the control group and 1 participant in the trial group discontinued the follow-up period. Finally, statistical analysis was performed on 58 patients (fig 1).

Interventions

The patients preoperatively and after catheterization received 10 mL/kg of the crystalloid ringer lactate solution in the

central artery and vein. Anesthesia was induced with 10-15 µg/kg of fentanyl and 0.1 mg/kg of midazolam; additionally, 0.1 mg/kg of pancuronium bromide was bolus-injected every 45 minutes for endotracheal intubation ease. The patients received 5 µg/kg/h of fentanyl and 1 µg/kg/min of midazolam as the maintenance dose. Mechanical ventilation was regulated on the respiratory tidal volume, and $PaCO_2$ was maintained between 30 mm Hg and 35 mm Hg.

The trial group received dexmedetomidine (0.5 µg/kg) via a bolus injection in 10 minutes and then a dexmedetomidine infusion (0.5 µg/kg/h) until the end of surgery. In the same way, the control group received the normal saline solution. Heart rate, systolic and diastolic pressure, and central venous pressure were measured prior to surgery, before and after the intervention, after skin incision, following the sternotomy, after surgery, and following pump weaning. Moderate hypothermia and whole fresh blood were used to achieve a hematocrit level between 25% and 30%. The mean arterial pressure was kept between 40 mm Hg and 70 mm Hg. Moreover, the total bypass time and the aortic cross-clamp time were measured. Hypotension and hypertension during pump usage were treated with phenylephrine and TNG, and their dosages were recorded in the trial checklist.

Trial Outcomes

Total antioxidant capacity (and malondialdehyde were measured in serum samples obtained with arterial catheters before the intervention, after pomp weaning, and 1 day later at the intensive care unit (ICU) as trial outcomes. For the measurement of biochemical parameters, 10 mL of peripheral blood samples were collected in heparinized tubes and sent to the laboratory.

Statistical Analysis

The collected data were entered into the SPSS software V19 (IBM Corporation, US) for statistical analysis. Quantitative and qualitative variables were presented as mean ± standard deviation and frequencies and percentages, respectively. The normality of the frequency distribution of the study samples was assessed using the Shapiro-Wilk test, and the independent samples *t* test and the Man-Whitney *U* test were employed to compare variables between the trial and control groups in parametric and nonparametric analyses. All *P* values less than 0.05 were considered significant.

RESULTS

Finally, 58 participants, including 37 men, were analyzed. The mean age and the mean body mass index were 59.62±9.68 years and 27.15±4.94 kg/m^2, respectively. The study samples were randomly allocated to trial (30, 52.7%) and control (28, 48.3%) groups. Among background disorders, hypertension (34, 58.6%) and diabetes (24, 41.4%) had the highest frequencies, and renal impairment (2, 3.4%) and thyroid disorders (1, 1.6%) had the lowest frequencies. No significant differences were observed concerning the study variables between the groups at pre and postoperative times (Table 1 & Table 2).

A comparison of endogenous antioxidant parameters demonstrated that all these parameters were higher in the trial group than in the control group; nonetheless, the differences were not statistically significantly different (Table 3).

Concerning surgery-related complications, 1 patient in each of the 2 study groups needed a defibrillator, but the groups were not statistically different in this regard (*P* =0.96). Similarly, the rate of temporary pacemaker usage (*P* =0.97) and bleeding (*P* =0.65) showed no significant differences between the 2 study groups. The mean blood drainage volume was similar in the trial and control

groups (521.67±418.88 mL vs 503.57±339.64 mL; *P* =0.86). The mean diuresis (745.01±482.87 vs 707.14±295.24; *P* =0.72) and hemofiltration (224.14±491.103 vs 446.43±667.490; *P* =0.16) during cardiopulmonary bypass did not significantly differ between the 2 groups (Table 4).

Table 1: Comparison of the study variables between the 2 study groups before and after surgery

Groups / Variable	Control (n=28)	Trial (n=30)	*P* value
Male (%)	19 (51.4)	18(48.6)	0.53
Age (mon)	57.14±10.95	61.93±7.83	0.06
BMI (kg/m^2)	27.56±4.59	26.77±5.29	0.54
Bypass time (min)	73.93±25.38	78.76±23.54	0.46
Cross-clamp time (min)	39.68±15.32	43.97±13.02	0.26
Operation time (h)	4.59±0.81	5.16±1.09	0.40
Ventilation time	13.09±6.58	15.68±14.47	0.39
ICU stay (d)	3.29±1.31	3.62±2.59	0.54
Preoperative EF (%)	48.93±7.98	45.01±10.42	0.11
Postoperative EF (%)	40.01±10.80	50.01±5.01	0.18
Preoperative HR	72.11±12.55	73.33±10.23	0.68
Postoperative HR	81.04±12.41	86.66±8.75	0.77
Postoperative HR (1 d)	78.96±12.02	79.83±10.16	0.06
Preoperative CVP	9.29±2.62	10.03±3.47	0.36
Postoperative CVP	8.46±2.63	8.43±2.92	0.97
Postoperative CVP (1 d)	17.93±4.39	15.03±3.16	0.07

BMI, Body mass index; ICU, Intensive care unit; EF, Ejection fraction; HR, Heart rate; CVP, Central venous pressure

Table 2: Comparison of laboratory variables between the 2 study groups before and after surgery

Groups / Variable	Control (n=28)	Trial (n=30)	*P* value
Preoperative BUN	18.86±7.55	19.53±8.46	0.75
Postoperative BUN	18.42±8.27	19.40±7.20	0.64
Postoperative BUN (1 d)	20.01±10.93	21.97±89.94	0.46
Preoperative Cr	1.33±1.51	1.47±2.07	0.78
Postoperative Cr	1.19±1.54	0.99±0.47	0.50
Postoperative Cr (1 d)	1.37±1.86	1.15±0.48	0.53
Preoperative AST	22.30±20.05	18.67±6.54	0.35
Postoperative AST	35.50±13.41	36.73±10.77	0.70
Postoperative AST (1 d)	55.64±54.08	31.94±5.83	0.84
Preoperative ALT	23.37±13.27	21.43±14.19	0.59
Postoperative ALT	22.89±17.09	23.01±11.77	0.98
Postoperative ALT (1 d)	24.11±19.75	33.80±10.27	0.94

BUN, Blood urea nitrogen; Cr, Creatinine; AST, Aspartate aminotransferase; ALT, Alanine transaminase

Table 3: Frequency distribution of endogenous antioxidants among the study participants

Groups / Variable	Control (n=28)	Trial (n=30)	*P* value
TAC (baseline)	0.41±0.22	0.42±0.22	0.82
TAC (postoperative)	0.36±0.23	0.41±0.19	0.47
TAC (ICU)	0.35±0.13	0.34±0.15	0.90
MDA (baseline)	1.02±0.97	0.95±1.02	0.81
MDA (postoperative)	1.14±1.44	1.16±1.45	0.97
MDA (ICU)	2.31±4.09	0.96±1.11	0.09

TAC, Total antioxidant capacity; MDA, Malondialdehyde

Table 4: Frequency distribution of coagulative factors among the study participants

Variable \ Groups	Control (n=28)	Trial (n=30)	*P* value
Epinephrine in the operating room	0.32±0.48	0.37±0.49	0.72
Epinephrine at the ICU	0.21±0.42	0.27±0.45	0.25
Norepinephrine in the operating room	0.04±0.19	-	0.31
Norepinephrine at the ICU	0.07±0.26	-	0.33
Milrinone in the operating room	0.04±0.19	-	0.31
Milrinone at the ICU	0.04±0.19	-	0.31
PC in the operating room	1.8202±1.42	1.01±0.48	0.70
PC at the ICU	1.01±1.06	1.20±0.48	0.55
FFP in the operating room	0.25±0.15	0.5±0.94	0.28
FFP at the ICU	0.29±0.76	0.71±1.26	0.28

ICU, Intensive care unit; FFP, Fresh frozen plasma

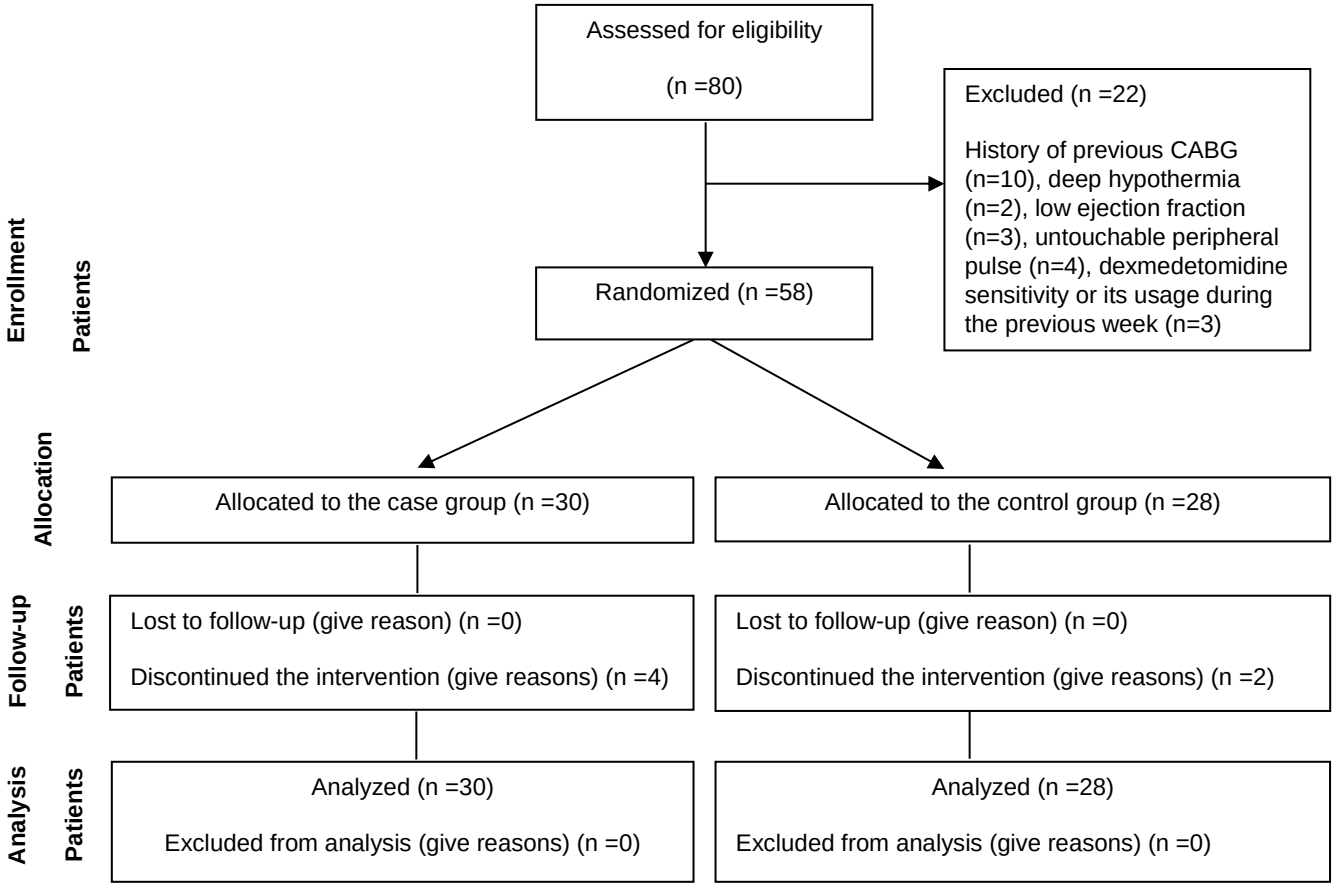

Figure 1: The image depicts the flow diagram of the study participants.

DISCUSSION

The results of the present study conducted on 58 patients demonstrated that only total antioxidant capacity and malondialdehyde at the third measurement point at the ICU were lower in the trial group than in the control group. The levels of other endogenous antioxidants were higher in the trial group than in the control group. No significant differences were detected in endogenous antioxidant levels between the trial and control groups.

Dexmedetomidine is a highly selective α-2 adrenergic receptor agonist and is used as an analgesic and anesthetic agent in clinical practice. [18] This drug has anti-inflammatory and antioxidant effects on vital organs, such as the heart, [19,20] lungs, [21,22] and kidneys. [23] Dexmedetomidine has anti-inflammatory effects and plays a protective role against oxidative damage occurring *in vitro* and *in vivo*. [24,25]

Ischemia and mechanical stress, especially in organs such as the heart, might lead to oxidative stress, known as an imbalance between reactive oxygen species production and free radicals and inappropriate antioxidant function. [26] After tissue damage or trauma, a stress response is produced by the hypothalamus-pituitary-adrenal axis due to metabolic and hormonal changes. The response contains a wide range of endocrinology, hematology, and immunological changes. [27] The operative stress response is caused by pituitary hormone secretion and sympathetic nervous system activation. [28] More than anti-inflammatory impacts, dexmedetomidine has dose-dependent sedation and antianxiety effects, comparable with GABAergic agents, such as midazolam and propofol. [29-32] Dexmedetomidine decreases anesthesia induction with intravenous anesthetic drugs and opioid use during surgery, lessens the preoperative catecholamine concentration, and confers hemodynamic and sympathetic stability. [33,34] Similar studies have shown that dexmedetomidine might decrease cardiovascular risks, such as myocardial ischemia, and stimulate α-adrenergic receptors, leading to vasoconstrictive impacts on the epicardial arteries and improving endocardial perfusion. On the other hand, dexmedetomidine, as an ideal anesthetic drug, can modulate coronary blood flow and confer desirable anesthesia in patients undergoing CABG.

CONCLUSIONS

Dexmedetomidine as a bolus induction before CABG and as an infusion during CABG with CPB can improve endocardial blood flow and hemodynamic stability.

REFERENCES

1. Sadeghpour Tabaei A, Mortazian M, Yaghoubi A, Gorjipour F, Arasteh Manesh S, Totonchi Z, et al. Modified Ultrafiltration in Coronary Artery Bypass Grafting: A Randomized, Double-Blinded, Controlled Clinical Trial. Iran Red Crescent Med J. 2018; 20(5):e6.6187

2. Gorjipour F, Dehaki MG, Totonchi Z, Hajimiresmaiel SJ, Azarfarin R, Pazoki-Toroudi H, et al. Inflammatory cytokine response and cardiac troponin I changes in cardiopulmonary bypass using two cardioplegia solutions; del Nido and modified St. Thomas': a randomized controlled trial. Perfusion. 2017; 32(5):394-402.

3. Gorjipour F, Totonchi Z, Gholampour Dehaki M, Hosseini S, Tirgarfakheri K, Mehrabanian M, et al. Serum levels of interleukin-6, interleukin-8, interleukin-10, and tumor necrosis factor-α ,renal function biochemical parameters and clinical outcomes in pediatric cardiopulmonary bypass surgery. Perfusion. 2019; 34(8):651-9.

4. Gorjipour F, Saeedzadeh T, Tolouei tabar Y, Kachoueian N, Bahlouli Ghashghaei S, Mortazian M, et al. Remote ischemic preconditioning effects on inflammatory markers and myocardial protection in coronary artery bypass graft surgery. Perfusion. 2020:0267659120979293.

5. Adamik B, Kübler A, Gozdzik A, Gozdzik W. Prolonged cardiopulmonary bypass is a risk factor for intestinal ischaemic damage and endotoxaemia. Heart, Lung and Circulation. 2017; 26(7):717-23.

6. Doğan A, Türker FS. The Effect of On-Pump and Off-Pump Bypass Surgery on Arginase Activity and Nitric Oxide Level.

7. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology. 2000; 93(2):382-94.

8. Gellai M, Ruffolo RR, Jr. Renal effects of selective alpha-1 and alpha-2 adrenoceptor agonists in conscious, normotensive rats. J Pharmacol Exp Ther. 1987; 240(3):723-8.

9. Biccard BM, Goga S, de Beurs J. Dexmedetomidine and cardiac protection for non-cardiac surgery: a meta-analysis of randomised controlled trials. Anaesthesia. 2008; 63(1):4-14.

10. Devereaux PJ, Investigators P-. Rationale and design of the PeriOperative ISchemic Evaluation-2 (POISE-2) trial: an international 2 x 2 factorial randomized controlled trial of acetyl-salicylic acid vs placebo and clonidine vs placebo in patients undergoing noncardiac surgery. Am Heart J . 9-804:(6)167;2014e4.

11. Frumento RJ, Logginidou HG, Wahlander S, Wagener G, Playford HR, Sladen RN. RETRACTED: Dexmedetomidine infusion is associated with enhanced renal function after thoracic surgery. Elsevier; 2006.

12. Mehrabanian MJ, Dehghani Firoozabadi M, Ahmadi Tafti SH, Forouzan Nia SK, Najafi A, Mortazian M, et al. Clinical Outcomes and Electrolyte Balance Factors in Complex Cardiac Operations in Adults; Del Nido® Versus Custodiol® Cardioplegia Solutions: A Randomized Controlled Clinical Trial . Iran Red Crescent Med J. 2018; 20(4):e64648.

13. Mehrabanian MJ, Firoozabadi MD, Tafti SHA, Nia SKF, Najafi A, Mortazian M, et al. Clinical outcomes and electrolyte balance factors in complex cardiac operations in adults; del nido versus custodiol cardioplegia solutions: a randomized controlled clinical trial. Iranian Red Crescent Medical Journal. 2018; 20(4).

14. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology. 1992; 77(6.42-1134)

15. Chiu TH, Chen MJ, Yang YR, Yang JJ, Tang FI. Action of dexmedetomidine on rat locus coeruleus neurones: intracellular recording in vitro. Eur J Pharmacol. 1995; 285(3):261-8.

16. Farsad BF, Janipour M, Totonchi Z, Gorjipour F, Oroji Omid S. Effects of dexmedetomidine on surgical stress responses at patients under CABG. Biosciences Biotechnology Research Asia. 2016; 13(3):1537-45.

17. Ammar AS, Mahmoud KM, Kasemy ZA, Helwa MA. Cardiac and renal protective effects of dexmedetomidine in cardiac surgeries: A randomized controlled trial. Saudi J Anaesth. 2016; 10(4):395-401.

18. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg. 2000; 90(3):699-705.

19. Gao JM, Meng XW, Zhang J, Chen WR, Xia F, Peng K, et al. Dexmedetomidine Protects Cardiomyocytes against Hypoxia/Reoxygenation Injury by Suppressing TLR4-MyD88-NF-kappaB Signaling. Biomed Res Int. 2017; 2017:1674613.

20. Ibacache M, Sanchez G, Pedrozo Z ,Galvez F, Humeres C, Echevarria G, et al. Dexmedetomidine preconditioning activates pro-survival kinases and attenuates regional ischemia/reperfusion injury in rat heart. Biochim Biophys Acta. 2012; 1822(4):537-45.

21. Cui J, Zhao H, Yi B, Zeng J, Lu K, Ma D. Dexmedetomidine Attenuates Bilirubin-Induced Lung Alveolar Epithelial Cell Death In Vitro and In Vivo. Crit Care Med. 2015; 43(9):e356-68.

22. Shen J, Fu G, Jiang L, Xu J, Li L, Fu G. Effect of dexmedetomidine pretreatment on lung injury following intestinal ischemia-reperfusion. Exp Ther Med. 2013; 6(6):1359-64.

23. Si Y, Bao H, Han L, Shi H, Zhang Y, Xu L, et al. Dexmedetomidine protects against renal ischemia and reperfusion injury by

inhibiting the JAK/STAT signaling activation. J Transl Med. 2013.11:141;

24. Zhang XY, Liu ZM, Wen SH, Li YS, Li Y, Yao X, et al. Dexmedetomidine administration before, but not after, ischemia attenuates intestinal injury induced by intestinal ischemia-reperfusion in rats. Anesthesiology. 2012; 116(5):1035-46.

25. Okada H, Kurita T, Mochizuki T, Morita K, Sato S. The cardioprotective effect of dexmedetomidine on global ischaemia in isolated rat hearts. Resuscitation. 2007; 74(3):538-45.

26. Devasagayam TP, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS, Lele RD. Free radicals and antioxidants in human health: current status and future prospects. J Assoc Physicians India. 2004; 52:794-804.

27. Desborough JP. The stress response to trauma and surgery. Br J Anaesth. 2000; 85(1):109-17.

28. Tsukada K, Katoh H, Shiojima M, Suzuki T , Takenoshita S, Nagamachi Y. Concentrations of cytokines in peritoneal fluid after abdominal surgery. Eur J Surg. 1993; 159(9):475-9.

29. Vertanen R, Savola J, Sano V, Nyman L. Characterization of selectivity, specificity and potency of medetomidine as alpha-2 adrenoreceptor agonists. Eur J Pharmacol. 1988; 150:9-14.

30. Venn R, Bradshaw C, Spencer R, Brealey D, Caudwell E, Naughton C, et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit .Anaesthesia. 1999; 54(12):1136-42.

31. Virtanen R, Savola J-M, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an α2-adrenoceptor agonist. European journal of pharmacology. 1988; 150(1-2):9-14.

32. McDonald T, Hoffman WE, Berkowitz R, Cunningham F, Cooke B. Heart rate variability and plasma catecholamines in patients during opioid detoxification. Journal of neurosurgical anesthesiology. 1999; 11(3):195-9.

33. Kallio A, Scheinin M, Koulu M, Ponkilainen R, Ruskoaho H, Viinamäki O, et al. Effects of dexmedetomidine, a selective α2-adrenoceptor agonist, on hemodynamic control mechanisms. Clinical Pharmacology & Therapeutics. 1989; 46(1):33-42.

34. Scheinin M, Kallio A, Koulu M, Viikari J, Scheinin H. Sedative and cardiovascular effects of medetomidine, a novel selective alpha 2-adrenoceptor agonist, in healthy volunteers. British journal of clinical pharmacology. 1987; 24(4):443-51.