Original Article

The myocardial protective effect of dexmedetomidine in high-risk patients undergoing aortic vascular surgery

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ABSTRACT

Objective: The aim of the study was to assess the effect of dexmedetomidine in high-risk patients undergoing aortic vascular surgery. **Design:** A randomized prospective study. **Setting:** Cairo University, Egypt. **Materials and Methods:** The study included 150 patients undergoing aortic vascular surgery. **Intervention:** The patients were classified into two groups ($n = 75$). Group D: The patients received a loading dose of 1 μg/kg dexmedetomidine over 15 min before induction and maintained as an infusion of 0.3 μg/kg/h to the end of the procedure. Group C: The patients received an equal volume of normal saline. The medication was prepared by the nursing staff and given to anesthetist blindly. **Measurements:** The monitors included the heart rate, mean arterial blood pressure, central venous pressure, electrocardiogram (ECG), serum troponin I level, end-tidal sevoflurane, and total dose of morphine in addition transthoracic echocardiography to the postoperative in cases with elevated serum troponin I level. **Main Results:** The dexmedetomidine decreased heart rate and minimized the changes in blood pressure compared to control group ($P < 0.05$). Furthermore, it decreased the incidence of myocardial ischemia reflected by troponin I level, ECG changes, and the development of new regional wall motion abnormalities ($P < 0.05$). Dexmedetomidine decreased the requirement for nitroglycerin and norepinephrine compared to control group ($P < 0.05$). The incidence of hypotension and bradycardia was significantly higher with dexmedetomidine ($P < 0.05$). **Conclusion:** The dexmedetomidine is safe and effective in patients undergoing aortic vascular surgery. It decreases the changes in heart rate and blood pressure during the procedures. It provides cardiac protection in high-risk patients reflected by decreasing the incidence of myocardial ischemia and serum level of troponin. The main side effects of dexmedetomidine were hypotension and bradycardia.

Received: 26-03-16
Accepted: 06-08-16

Key words: Aortic vascular surgery; Dexmedetomidine; Myocardial ischemia; Myocardial protection; Troponin I

INTRODUCTION

The patients undergoing vascular surgery are usually high-risk cases because of the associated coexisting diseases such as coronary artery disease, hypertension, and diabetes mellitus. Cross-clamping and declamping of the aorta may lead to profound homeostatic disturbance and the risk of circulatory decompensation.[1,2]

The incidence of postoperative myocardial infarction after supraceliac clamping for thoracoabdominal aortic aneurysm surgery is 7%, whereas the postoperative cardiac complications without evidence of ischemic damage are 36%, such as pulmonary edema, arrhythmias, or decreased cardiac output.[3,4] Furthermore, the infrarenal aortic

Access this article online
Website: www.annals.in
DOI: 10.4103/0971-9784.191570
Quick Response Code:

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Cite this article as: Soliman R, Zohry G. The myocardial protective effect of dexmedetomidine in high-risk patients undergoing aortic vascular surgery. Ann Card Anaesth 2016;19:606-13.

cross-clamping is associated with myocardial ischemia.[5] Previous reports found a rise in cardiac troponin I with elective surgical aortic aneurysm repair.[2,6] Subclinical myocardial injury after major vascular surgery is common and detected by a rise in cardiac troponin and is associated with increased mortality.[7,8]

Dexmedetomidine is a highly selective α-2-agonist that induces anxiolysis and analgesia without respiratory depression.[9] It decreases plasma norepinephrine,[10] the stress response to surgery and intensive care procedures, and provides perioperative cardiac protection in patients with coronary risk factors,[11-13] by decreasing the heart rate and blood pressure, therefore, improving oxygen supply and demand balance;[14] therefore, the present study was done to evaluate the perioperative myocardial protective effect of dexmedetomidine in high-risk patients undergoing aortic vascular surgery.

PATIENTS AND METHODS

After approval of the Local Ethics Committee and obtaining written informed consent in Kasr El-Aini Hospital, Cairo University, Egypt, a double-blind, randomized study included 150 patients (American Society of Anesthesiology [ASA] physical status III–IV) undergoing elective aortic surgery (aortic aneurysm or aortobifemoral anastomosis) (2013–2015). Exclusion criteria included patients with acute myocardial infarction, congestive heart failure, heart block, obese patients, or emergency. All patients were evaluated preoperatively by cardiologists and anesthesiologists. Preoperatively, the transthoracic echocardiography was done for all patients (to assess the valvular function, contractility, or the presence of regional wall motion abnormalities). All preoperative medications were given regularly. Patients on anticoagulants were managed by cardiologist preoperatively. The patients classified randomly (by simple randomization) into two groups (n = 75 each): Group D: The patients received a loading dose of 1 μg/kg dexmedetomidine over 15 min before induction and maintained as an infusion of 0.3 μg/kg/h to the end of the procedure.

Group C: The patients received an equal volume of normal saline. The medication was prepared by the nursing staff and given to anesthetist blindly.

Anesthetic technique

For all patients and under local anesthesia, a radial arterial cannula and central venous line were inserted. An epidural catheter was inserted through the L3–L4 intervertebral space before anesthesia induction, and another epidural catheter was inserted in the subarachnoid space L4–L5 for withdrawal of cerebrospinal fluids (10 ml/h to maintain an intrathecal pressure of 10 cm H_2O or less,[15,16] and injection of cold saline for the protection of the spinal cord in cases of thoracic aortic surgery (during the procedures only). After preoxygenation with 100% oxygen, anesthesia was induced gently with intravenous fentanyl (1–2 μg/kg), thiopental (3–5 mg/kg), and atracurium (0.5 mg/kg). The double lumen endotracheal tube was needed for one lung ventilation in cases of thoracic aortic surgery and changed by a simple tube after surgery. After tracheal intubation and starting of mechanical ventilation, the anesthesia was maintained with sevoflurane (1–3%), fentanyl infusion (1–3 μg/kg/h), atracurium (0.5 mg/kg/h), and oxygen:air (50:50%) in addition to epidural infusion of bupivacaine (loading dose of 1–1.5 ml/segment, 0.125% bupivacaine to a T4 sensory level, and a continuous infusion of 0.125% bupivacaine without opioid at 4 ml/h). Hypertension during clamping was managed with bolus doses of fentanyl, increasing the concentration of sevoflurane, or the addition of nitroglycerin infusion. Hypotension was managed with fluids, bolus doses of ephedrine, or decreasing sevoflurane concentration in addition to norepinephrine after declamping if needed. Bradycardia was managed with bolus doses of atropine (30 μg/kg). Patients with thoracic aortic surgery received crystalloids (500–1000 ml), mannitol 20% (100 ml), and furosemide (40 mg) through 30 min before clamping for renal protection.

The patients were transferred to postanesthesia care unit with close monitoring and observation for 2–4 h or Intensive Care Unit according to the preoperative plan. The cases of thoracic aortic surgery were ventilated postoperatively for 2–3 days.

Monitoring of patients

The monitors included heart rate, mean arterial blood pressure, central venous pressure, a continuous electrocardiograph with automatic ST-segment analysis (leads II and V), arterial oxygen saturation, temperature, urinary output, end-tidal sevoflurane, total dose of fentanyl, and arterial blood gasses. Hemodynamic values were serially collected at the following: At baseline, after induction of anesthesia, every 5 min during the procedure, at the end of surgery, and every 5 min in the postanesthetic care unit or Intensive Care Unit. The cardiac enzyme troponin I was measured before administration of study medication at

12th, 24th, and 48th h postoperatively. Postoperatively, the transthoracic echocardiography was done for cases with ischemic changes in the electrocardiogram (ECG) and elevated troponin I.

Sample size calculation

Power analysis was performed using Chi-square test for independent samples on the frequency of patients complaining of postoperative myocardial problems after aortic vascular surgery because it was the main outcome variable in the present study. A pilot study was done before starting this study because there are no available data in the literature for the role of dexmedetomidine in high-risk cardiac patients undergoing aortic vascular surgery. The results of the pilot study showed that the incidence of hemodynamic instability was 11.3% in dexmedetomidine group and 30% in control group. Taking power 0.8 and alpha error 0.05, a minimum sample size of 72 patients was calculated for each group. A total of patients in each group 75 were included to compensate for possible dropouts.

The statistical analysis

Data were statistically described in terms of mean ± standard deviation or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student's *t*-test for independent samples. Within-group comparison of numerical variables was done using paired *t*-test. For comparing categorical data, Chi-square test was performed. Fisher's exact test was used instead when the expected frequency is <5. $P < 0.05$ was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

RESULTS

Table 1 shows no difference regarding the demographic data, preoperative comorbidity, medications, ejection fraction, and ASA physical status of patients ($P > 0.05$).

Table 2 shows no difference in the heart rate before starting the study medication (T0). The heart rate decreased significantly in Group D patients at timepoints T1–T7 in comparison to the preoperative value ($P < 0.05$), but the heart rate increased significantly in Group C patients at timepoints T1–T7 in comparison to the preoperative value ($P < 0.05$), and the comparison between the two groups was significant ($P < 0.05$).

Table 1: Preoperative data of patients

Item	Group D (*n*=75)	Group C (*n*=75)	*P*
Age (year)	58.37±7.32	57.82±7.65	0.656
Weight (kg)	81.04±9.50	82.64±9.17	0.986
Gender			
Female	40	35	0.533
Male	37	38	0.493
Hypertension	38	35	0.467
Diabetes mellitus	21	25	0.332
Ischemic heart disease	9	4	0.051
Cardiac surgery			
CABG	4	1	0.999
Bentall procedure	-	1	
Valvular	1	2	0.999
Beta blockers	29	26	0.346
Calcium channel blockers	17	12	0.159
ACEI	4	7	0.054
Aspirin	8	4	0.056
Beta blockers	29	26	0.346
Calcium channel blockers	17	12	0.159
Ejection fraction (%)	52.13±8.80	53.67±9.43	0.302
ASA classification			
II	36	39	0.481
III	40	35	0.533

Data are presented as mean±SD, number (%). Old MI: Old myocardial infarction, CABG: Coronary artery bypass grafting, ACEI: Angiotensin-converting enzyme inhibitors, ASA: American Society of Anesthesiology, SD: Standard deviation

Table 2: Heart rate of patients

Time points	Group D (*n*=75)	Group C (*n*=75)	*P*
T0	79±8	77±8	0.838
T1	73±6†	88±10†	0.001*
T2	73±5†	88±10†	0.001*
T3	74±5†	87±9†	0.001*
T4	73±5†	87±9†	0.001*
T5	72±6†	89±7†	0.001*
T6	72±6†	84±8†	0.002*
T7	73±5†	87±7†	0.001*

Data are presented as mean±SD. *P<0.05 significant comparison between the two groups, †P<0.05 significant compared to the preoperative reading within the same group. T0: Preoperative reading before study medication, T1: Reading 15 min after induction, T2: Reading before clamping, T3: Reading before declamping, T4: Reading 15 min after declamping, T5: Reading at end of surgery, T6: Reading at 1 h in the postanesthesia care unit or ICU, T7: Reading after 2 h in the postanesthesia care unit or ICU. SD: Standard deviation, ICU: Intensive Care Unit

Table 3 shows no difference in the mean arterial blood pressure before administration of study medication (T0). Group D showed no significant difference in the mean arterial blood pressure through various timepoints in

comparison to the preoperative value ($P > 0.05$), but the mean arterial blood pressure increased significantly in Group C patients at timepoints T1–T7 in comparison to the preoperative value ($P < 0.05$), and the comparison between the two groups was significant ($P < 0.05$).

Table 4 shows no significant difference in central venous pressure between the two groups ($P > 0.05$).

Table 5 shows no difference in the type of surgery, durations of aortic cross-clamping, and surgery ($P > 0.05$). The incidence of hypotension before aortic clamping was higher in Group D compared to Group C, but statistically insignificant ($P = 0.067$). After aortic declamping, the incidence of hypotension was significantly higher in Group C compared to Group D ($P = 0.001$). The incidence of hypertension after induction and before aortic cross-clamping was significantly lower in Group D compared with Group C ($P = 0.034$). The incidence of bradycardia during the procedure was significantly higher in Group D compared with Group C ($P = 0.011$). During aortic cross-clamping, the nitroglycerin was required in Group C patients more than Group D ($P = 0.001$), and after declamping, norepinephrine was required in Group C patients more than Group D ($P = 0.048$). The required amount of fluids (crystalloid and colloids) was less in Group D than Group C patients ($P < 0.05$), but no difference in the transfused blood products ($P > 0.05$). The total dose of fentanyl and end-tidal sevoflurane concentration was significantly lower in Group D patients compared with Group C ($P = 0.001$, $P = 0.015$, respectively).

Table 3: Mean arterial blood pressure of patients

Time points	Group D (*n*=75)	Group C (*n*=75)	*P*
T0	99±10	97±8	0.882
T1	98±9†	109±8†	0.001*
T2	104±10†	114±11†	0.001*
T3	105±10†	115±10†	0.001*
T4	101±9†	110±10†	0.001*
T5	100±9†	107±8†	0.045*
T6	99±8†	110±9†	0.002*
T7	98±8†	105±9†	0.032*

Data are presented as mean±SD. **P*<0.05 significant comparison between the two groups, †*P*<0.05 significant compared to the preoperative reading within the same group. T0: Preoperative reading before study medication, T1: Reading 15 min after induction, T2: Reading before clamping, T3: Reading before declamping, T4: Reading15 min after declamping, T5: Reading at end of surgery, T6: Reading at 1 h in the postanesthesia care unit or ICU, T7: Reading after 2 h in the postanesthesia care unit or ICU. SD: Standard deviation, ICU: Intensive Care Unit

Table 4: Central venous pressure of patients

Time points	Group D (*n*=75)	Group C (*n*=75)	*P*
T0	10.84±2.21	10.69±2.26	0.688
T1	10.66±1.60	10.86±1.45	0.341
T2	10.48±1.99	10.84±2.09	0.283
T3	10.70±1.73	10.93±2.10	0.479
T4	10.85±1.60	10.93±2.17	0.796
T5	10.80±1.83	11.06±2.14	0.414
T6	11.18±1.79	10.78±1.83	0.135
T7	11.09±1.55	10.97±1.97	0.680

Data are presented as mean±SD. T0: Preoperative reading before study medication, T1: Reading 15 min after induction, T2: Reading before clamping, T3: Reading before declamping, T4: Reading 15 min after declamping, T5: Reading at end of surgery, T6: Reading at 1 h in the postanesthesia care unit or ICU, T7: Reading after 2 h in the postanesthesia care unit or ICU, SD: Standard deviation, ICU: Intensive Care Unit

Table 6 shows no difference in the preoperative troponin I level between the two groups ($P = 0.118$), but increased significantly at 12th, 24th, and 48th h in 17 patients of Group C compared with 4 patients in Group D ($P = 0.015$, $P = 0.012$, and $P = 0.043$, respectively). There were postoperative ischemic changes in the ECG (depressed or elevated ST segment) in both groups during the study. The incidence of ischemia was three patients in Group D and 14 patients in Group C ($P = 0.004$), and the incidence of myocardial infarction was only one case in Group D and three cases in Group C ($P = 0.536$). The transthoracic echocardiography was done and showed the development of new regional wall motion abnormalities in 4 patients in Group D and 17 patients in Group C ($P = 0.002$). These patients were managed in Intensive Care Units with nitroglycerin and inotropic support to maintain hemodynamic stability until the ECG changes and troponin level become normal. There was no mortality as results of myocardial ischemia or infarction. There was no renal failure in both groups, but the creatinine level increased in four patients of Group D and six patients of Group C ($P = 0.746$). There was only one case suffered from intestinal ischemia in Group C. The pulmonary complication (infection and edema) was only in one patient of Group D and two patients of Group C ($P = 0.999$). There were no neurological complications in both groups. The incidence of mortality was only one case in Group C (this patient suffered from intestinal ischemia) and no case in Group D.

Table 5: Intraoperative data of patients

Item	Group D (*n*=75)	Group C (*n*=75)	*P*
Cross-clamping duration (min)	123±7	123±8	0.732
Duration of surgery (min)	238.3±11.03	236.82±10.85	0.654
Hypotension (%)			
Before clamping	7(9.3)	3(4)	0.067
After declamping	10(13.3)	21(28)	0.001
Hypertension before clamping	3(4)	9(12)	0.034
Bradycardia	9(12)	2(2.6)	0.011
Nitroglycerine during clamping			
Number (%)	3(4)	14(18.6)	0.001
Dose (μg/kg/min)	0.40±0.21	2.21±0.50	0.001
Total dose (mg)	3.99±0.02	22.58±0.04	0.001
Norepinephrine after declamping			
Number (%)	5(6.6)	21(285)	0.001
Dose (μg/kg/min)	0.04±0.02	0.07±0.05	0.048
Total dose (mg)	0.42±0.01	0.74±0.01	0.001
Fluids (ml)			
Crystalloids	3614±601	4505±578	0.001
Colloids	751±235	1081±275	0.014
PRBC	971±267	931±245	0.344
FFP	460±126	484±131	0.273
End-tidal sevoflurane (%)	1.22±0.28	2.03±0.31	0.015
Total dose of fentanyl (μg)	370±113	531±126	0.001
Type of surgery (%)			
Thoracic aortic aneurysm repair	17(22.6)	14(18.6)	0.185
Thoracobifemoral anastomosis	9(12)	7(9.3)	0.118
Abdominal aortic aneurysm repair	24(32)	28(37.3)	0.319
Aortobifemoral anastomosis	25(33.3)	26(34.6)	0.334

Data are presented as mean±SD, number (%). PRBC: Packed red blood cell, FFP: Fresh frozen plasma, SD: Standard deviation

Table 6: Postoperative outcomes

Item	Group D (*n*=75)	Group C (*n*=75)	*P*
Troponin I (ng/ml)			
Preoperative	0.56±0.16	0.50±0.29	0.118
12th h			
Number	4	17	0.002*
Mean	1.46±0.15†	1.70±0.18†	0.015*
24th h			
Number	4	17	0.002*
Mean	1.41±0.12†	1.62±0.16†	0.0123*
48th h			
Number	4	17	0.002*
Mean	1.38±0.10†	1.51±0.12†	0.043*
Myocardial ischemia	3	14	0.004
Myocardial infarction	1	3	0.536
New regional wall motion abnormalities	4	17	0.002*
Renal			
Impairment (creatinine >115 μmol/L)	4	6	0.746
Failure	-	-	
Intestinal ischemia	-	1	
Pulmonary complications (infection and edema)	1	2	0.999
Neurological complications	-	-	
Mortality	0	1	

Data are presented as mean±SD, number. 12th h: 12th postoperative hour, 24th h: 24th h postoperative hour, 48th h: 48th postoperative hour. **P*<0.05 significant comparison between the two groups. †*P*<0.05 significant compared to the preoperative reading within the same group, Myocardial ischemia: Ischemia of the myocardial associated with ST-segment changes without elevation in troponin level, Myocardial infarction: Myocardial injury as a result of myocardial ischemia and associated with ST-segment changes and elevated troponin level. SD: Standard deviation

DISCUSSION

The present study showed that dexmedetomidine decreased the heart rate and minimized the fluctuations in the arterial blood pressure before, during, and after aortic cross-clamping. Therefore, dexmedetomidine led to keeping the balance of oxygen supply/demand ratio and minimizing the incidence of myocardial ischemia and infarction reflected by the ECG changes, postoperative troponin I level, and the development of new regional wall motion abnormalities compared to control group. Furthermore, dexmedetomidine decreased the requirement for nitroglycerin and norepinephrine during the procedures; thus, it minimized the changes in hemodynamics, and therefore, dexmedetomidine provided myocardial protection in high-risk patients during aortic surgery.

Perioperative hypertension and tachycardia are common hemodynamic disturbances in patients undergoing abdominal aortic surgery. Aortic cross-clamping is associated with an increase in systemic vascular resistance, pulmonary capillary wedge pressure, and a decrease in cardiac index and causes myocardial ischemia.[17] Dexmedetomidine suppresses the stress response to surgery by activation of peripheral α-2 receptors and reducing the release of catecholamines

and thus leads to minimizing the fluctuations in the hemodynamics.[18,19]

Marston *et al*.[20] reported in a cohort study included 182 patients who underwent aortic aneurysm repair that troponin I elevated in 58 patients (32%) with depressed ST-segment in the postoperative 48 h. Landesberg *et al*.[21] found that perioperative ischemic events are thought to be caused by oxygen supply-demand mismatch induced by the physiological stresses of surgery and recovery from anesthesia, and one study showed that dexmedetomidine decreases tissue metabolism and tissue oxygen demand in situations associated with tissue hypoxia.[22]

Willigers *et al*.[23] reported that anti-ischemic effects of dexmedetomidine in dogs were explained by increasing the endo-/epicardial ratio of blood flow, decreasing the plasma concentrations of norepinephrine, epinephrine, slower heart rate, and evidenced by a decreased prevalence of myocardial lactate release compared to the saline group ($P < 0.05$).

In a meta-analysis study (22 trials, 3395 patients), Wijeysundera *et al*.[24] investigated the effects of α-2 adrenergic agonists (clonidine, dexmedetomidine, or mivazerol) on adults undergoing surgery. They found that α-2 adrenergic agonists reduced myocardial infarction and mortality ($P = 0.020$) during vascular surgery. During cardiac surgery, α-2 adrenergic agonists reduced ischemia ($P = 0.01$) and were associated with trends toward decreased risk of myocardial infarction and mortality, and the same results were reported by Biccard *et al*.[14] and Wijeysundera *et al*.[25]

Landesberg *et al*.[26] monitored patients with continuous ECG in the perioperative period and they found that ST-segment depression was associated with increased heart rates, and the value of troponin elevation was strongly correlated with the duration of the ST depression.

Nair[27] showed that dexmedetomidine maintains stable hemodynamics during induction, intraoperatively, and during extubation of patients undergoing carotid endarterectomy, and Bekker *et al*.[28] found that dexmedetomidine reduced significantly the requirements for beta-blockers and antihypertensive drugs and minimized the fluctuation in hemodynamics in patients undergoing awake carotid endarterectomy. Ren *et al*.[29] showed that dexmedetomidine decreased the incidence of postoperative myocardial injury and level of cardiac enzymes (troponin and creatine kinase-MB) in patients undergoing off-pump coronary artery bypass grafting, and dexmedetomidine provided myocardial protection, and the same results were reported by Chi *et al*.[30] and Zhang *et al*.[31]

Against the present findings, Talke *et al*.[32] evaluated the effect of dexmedetomidine on patients (age 18–80 years, ASA II–III) undergoing aortic and peripheral vascular surgery. They found no difference in their hemodynamic response to intubation, skin incision, during the procedure, or extubation compared to placebo. Braz *et al*.[33] evaluated the effect of dexmedetomidine on the cardiovascular response during infrarenal aortic cross-clamping in sevoflurane-anesthetized dogs. Aortic cross-clamping increased the mean arterial blood pressure, systemic vascular resistance index, central venous pressure, and pulmonary artery occlusion pressure in the dexmedetomidine group more than the control group. Furthermore, the heart rate, cardiac index, and systemic oxygen transport index were lower with dexmedetomidine than in the control group. After aortic declamping, mean arterial pressure, systemic vascular resistance index, and central venous pressure were maintained higher with dexmedetomidine compared to control. The authors found that the observed effects might limit the use of dexmedetomidine in association with sevoflurane, specifically in patients with a reduced cardiovascular reserve during aortic surgery.

The present study recognizes some limitations such as being single center study, and the serum level of dexmedetomidine was not measured as the kits were not available in the main laboratory.

CONCLUSION

The dexmedetomidine is safe and effective in patients undergoing aortic vascular surgery. It decreases the changes in heart rate and blood pressure during the procedures. It provides cardiac protection in high-risk patients reflected by decreasing the incidence of myocardial ischemia, serum level of troponin level, and the development of new regional wall motion abnormalities. The main side effects of dexmedetomidine were hypotension and bradycardia.

Acknowledgments

The authors thank all anesthesia technicians in the operative rooms and all nurses in the postanesthesia care unit for their help to achieve this work.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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