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Effect of dexmedetomidine on diseased coronary vessel diameter and myocardial protection in percutaneous coronary interventional patients

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ABSTRACT

Introduction: Dexmedetomidine is an alpha-2 agonist used for conscious sedation. It has also been shown to have a myocardial protective effect in off-pump coronary artery bypass patients. The aim of the study was to assess the effect of dexmedetomidine for myocardial protection in percutaneous coronary interventional patients. **Methodology:** A total of 60 patients (group dexmedetomidine, *n* = 30 and group normal saline, *n* = 30) were enrolled in the study. Dexmedetomidine infusion (1 mcg/kg) over 15 min was given as a loading dose after coronary angiography in group dexmedetomidine (D) while normal saline was given in the control group (C) and later maintenance infusion was started at 0.5 mcg/kg/h in both the groups. Coronary vessel diameter was noted before (T0) and after (T1) loading dose of dexmedetomidine/saline in each group. Troponin T (Trop T) values were noted at baseline (T0), 6 h (T2), 12 h (T3) and 24 h (T4) after starting the loading dose. Hemodynamic variables (heart rate [HR] and blood pressure) were monitored at T0, T1, and at regular intervals till 2 h postprocedure. **Results:** Coronary vessel diameter and HR significantly decreased in group D as compared to control group ($P < 0.05$) whereas the decrease in Trop T at 6 h, 12 h, and 24 h were not statistically significant between the two groups. **Conclusion:** Dexmedetomidine decreases the coronary vessel diameter, but maintains the myocardial oxygen demand-supply ratio by decreasing the HR. The decrease in Trop T is statistically insignificant at the doses used.

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INTRODUCTION

Myocardial injury in acute myocardial infarction (MI) is due to both ischemic as well as reperfusion injury. Reperfusion can cause hyperkalemia,[1] arrhythmias and a rise in cardiac enzymes (Troponin I and T and creatinine phosphokinase-MB (CPK-MB)). A number of strategies have been used to prevent lethal myocardial reperfusion injury in patients undergoing percutaneous coronary interventional (PCI) procedures. Mechanical interventions include remote ischemic preconditioning, therapeutic hypothermia and therapeutic hyperoxemia, whereas pharmacological interventions include adenosine, anti-inflammatory agents, atrial natriuretic peptide, atorvastatin, erythropoietin, glucose insulin potassium therapy and sodium nitrite.[2]

Dexmedetomidine is a selective alpha-2 agonist which may shrink the coronary

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arteries and reduce coronary blood flow.[3,4] But at the same time, dexmedetomidine reduces heart rate (HR) and consequently the myocardial oxygen demand. Hence, we postulate that dexmedetomidine should maintain the myocardial oxygen demand-supply ratio. In addition, dexmedetomidine results in sympathetic blockade, as it affects the alpha-2 receptors in the central nervous system and restrains the release of central sympathetic neurotransmitter (predominantly norepinephrine).[5] Patients undergoing PCI have a lot of stress response and hence, dexmedetomidine may be useful to alleviate anxiety which can also decrease the oxygen demand and improve the oxygen demand-supply ratio.

Dexmedetomidine has been shown to have a protective effect on myocardial ischemia/reperfusion (I/R) injury in rats[6,7] and decreases the incidence of arrhythmias. However, there is limited literature on the effect of dexmedetomidine during I/R injury in PCI patients.

Hence, the aim of the study was to assess the effect of dexmedetomidine on coronary vessel diameter and myocardial protective effect in patients undergoing PCI.

METHODOLOGY

After Institutional Ethics Committee approval, a prospective double-blind randomized controlled trial was conducted. A sample size of 60 was calculated based on a previous study.[8]

Sixty patients undergoing elective PCI for acute MI with single vessel disease were randomized into Group D (dexmedetomidine) $n = 30$ and Group C (control) $n = 30$. Patients above the age of 70 years, ejection fraction (EF) of <40% and in cardiogenic shock were excluded from the study. All these patients were adequately beta-blocked in the ward. Patients were randomized on the basis of computer-generated randomization table. The randomization scheme was generated by using the website Randomization.com<http://www.randomization.com>. The computer-generated group number (D or C) was enclosed in serially numbered closed opaque envelope. A person not related to the study was asked to open the closed envelope containing computer-generated group number. The groups were as follows:

- Group D: Injection dexmedetomidine 1 mcg/kg was administered over 15 min as a loading dose and then 0.5 mcg/kg/h as maintenance infusion
- Group C: Injection 0.9% NaCl (started and maintained at the same rate as calculated for group D).

Immediately after coronary angiogram (T0), a baseline troponin T (Trop T) was sent for analysis and coronary vessel diameter was measured immediately distal to the obstruction in the diastolic phase. Then, dexmedetomidine or 0.9% NaCl infusion was started. After the loading dose and before initiation of coronary angioplasty (T1), coronary diameter was again measured in the same view to see the effect of dexmedetomidine on the coronary diameter. The infusion of dexmedetomidine was continued until 30 min postprocedure. Trop T was analysed at 6 h (T2), 12 h (T3), and 24 h (T4) after starting the loading dose.

HR and blood pressure (BP) were monitored every 5 min during the procedure and every 10 min postprocedure for 2 h.

Electrocardiogram (ECG) was recorded preprocedure, postprocedure, at 24 h, and 72 h for any new ECG changes and/or arrhythmias.

Statistical analysis was performed using MedCalc software version 12.2.1.0.(Ostend, Belgium). Intragroup analysis were done using paired Student's *t*-test, and unpaired Student's *t*-test was done for analysis between the two groups. Hemodynamic variables and Trop T values were expressed as mean ± SD. $P < 0.05$ was considered significant.

RESULTS

Thirty patients were included in each of the two groups. In group D, there were 18 males and 12 females, whereas in group C, there were 16 males and 14 females. All the patients were aged between 40 and 60 years. In group D, 25 patients had EF between 40 and 50% and five patients had EF between 51% and 60%. In Group C, 23 patients had EF between 40% and 50% and seven patients had EF between 51% and 60%.

The diameter of the coronary vessel decreased significantly by around 14% after loading dose of dexmedetomidine infusion ($P = 0.000$) whereas no such significant change was observed in the control group ($P = 0.25$) [Table 1].

HR also decreased significantly by around 13% after loading dose of dexmedetomidine infusion ($P = 0.000$), while the change in HR was not significant in the control group ($P = 0.59$) [Table 2].

There was a statistically significant decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP) after administering loading dose of dexmedetomidine, but no such decrease was observed in the control group [Tables 3a and b].

There was no statistically significant difference in the Trop T values at baseline (T0), 6 h (T2), 12 h (T3), and at 24 h (T4) between dexmedetomidine group and control group [Table 4].

Three patients in the control group had arrhythmias during the procedure and postprocedure, while none in the dexmedetomidine group had arrhythmias.

DISCUSSION

Reperfusion injury is defined as damage to the tissue caused when blood supply is restored to the ischemic or hypoxic area after a certain period. Similar type of injury occurs in the myocardium after an acute MI treated by PCI or fibrinolytic therapy.[9-11]

Reperfusion is associated with microvascular injury, particularly due to increased permeability of capillaries and arterioles. Activated endothelial cells produce more reactive oxygen free radicals but less nitric oxide after reperfusion. This imbalance causes an inflammatory response which is partially responsible for the damage caused by reperfusion injury.[12] White blood cells (WBCs) are carried to the reperfused area by restoration of blood flow which causes a release of inflammatory factors such as interleukins and free radicals.[13] These cause damage to the cellular proteins, DNA, and the plasma membrane, which may cause further release of more free radicals. These mediators may also act indirectly in redox signaling to initiate apoptosis. WBC may also obstruct the small capillaries by binding to their endothelium, worsening the ischemia.[13] Furthermore, the ischemic tissue has decreased free radical scavengers, which results in further tissue damage after reperfusion.

Other mechanisms postulated in reperfusion injury include calcium overload and depletion of high energy phosphate stores.[14-16]

Table 1: Diameter of the coronary vessel before and after administering loading dose of dexmedetomidine/normal saline

	Mean±SD	*P*
Diameter before dexmedetomidine (T0)	2.79±0.396	0.000
Diameter after loading dose of dexmedetomidine (T1)	2.39±0.455	
Diameter before NS (T0)	2.63±0.384	0.252
Diameter after loading dose of NS (T1)	2.61±0.388	

NS: Normal saline, SD: Standard deviation

Table 2: Heart rate before and after administering loading dose of dexmedetomidine/normal saline

	Mean±SD	*P*
HR before dexmedetomidine (T0)	86.77±18.522	0.000
HR after loading dose of dexmedetomidine (T1)	75.17±18.607	
HR before NS (T0)	89.50±6.857	0.593
HR after loading dose of NS (T1)	88.73±9.770	

NS: Normal saline, SD: Standard deviation, HR: Heart rate

Table 3a: Systolic blood pressure before and after administering loading dose of dexmedetomidine/ normal saline

	Mean±SD	*P*
SBP before dexmedetomidine (T0)	137.83±26.95	0.000
SBP after loading dose of dexmedetomidine (T1)	117.67±17.31	
SBP before NS (T0)	129.6±17.63	0.36
SBP after loading dose of NS (T1)	129.3±17.23	

SBP: Systolic blood pressure, NS: Normal saline

Table 3b: Diastolic blood pressure before and after administering loading dose of dexmedetomidine/normal saline

	Mean±SD	*P*
DBP before dexmedetomidine (T0)	76.83±15.86	0.000
DBP after loading dose of dexmedetomidine (T1)	66.33±13.11	
DBP before NS (T0)	75.5±10.25	0.46
DBP after loading dose of NS (T1)	75.8±10.38	

DBP: Diastolic blood pressure, NS: Normal saline, SD: Standard deviation

Table 4: Trop T values (ng/ml) at baseline, 6 h, 12 h, and 24 h after initiation of the drug

	Dexmedetomidine group	Control group	*P*
T0	1.38±2.86	2.02±2.29	0.34
T2	1.49±2.61	1.79±1.35	0.58
T3	1.21±1.95	1.29±0.87	0.85
T4	0.81±1.34	1.12±1.10	0.31

Hyperkalemia,[1] arrhythmias, and rise in cardiac enzymes (Trop I and T and CPK-MB) may help us in recognizing this reperfusion injury.

Dexmedetomidine being a selective alpha-2 agonist may cause coronary vasoconstriction. Yoshitomi *et al.*[17] and Okada *et al.*[18] showed that dexmedetomidine has a direct dose-dependent cardioprotective effect on reperfusion injury and high dose of dexmedetomidine had favorable subendocardial-to-subepicardial blood flow ratio resulting in better functional recovery from myocardial stunning.

Dexmedetomidine is an ideal sedative agent in cardiac patients[19] as it is a sympatholytic, reduces HR, and consequently the myocardial oxygen demand. It causes conscious sedation in which the patient is arousable when stimulated. Hence, it is beneficial to use dexmedetomidine for sedating the anxious cardiac PCI patients.

In the present study, the SBP and DBP have shown a statistically significant decrease in group D. This can be attributed to sympatholysis and anxiolysis.[20] However, the decrease in BP was never <20% of the baseline.

There was also a significant decrease in the coronary vessel diameter. However, there was no significant change in the levels of Trop T. Hence, the authors infer that myocardial damage has not occurred with the decrease in coronary vessel diameter in the dexmedetomidine group. Although the blood flow has decreased due to coronary vasoconstriction, simultaneously, the demand has also decreased by a significant decrease in HR caused by dexmedetomidine. Hence, dexmedetomidine maintains the demand-supply ratio in spite of decreasing the coronary vessel diameter.

In the present study, three patients of control group had arrhythmias during the procedure and postprocedure, while none in the dexmedetomidine group had arrhythmias. There is a probability that dexmedetomidine could have prevented arrhythmias caused by I/R in the study group, but the sample size is too small to conclude this.

Chi *et al.*[21] found that dexmedetomidine reduces myocardial damage in patients undergoing off-pump coronary artery bypass graft surgery as noted by a decrease in the myocardial enzymes in the dexmedetomidine group as compared to the control group. In the present study, there was no significant decrease in Trop T levels in patients who were given the same dose of dexmedetomidine as in the above study. This could be due to various reasons. First, the dosage of dexmedetomidine used was based on previous studies done in cardiac surgical patients. The dosage required in PCI patients may be different because of shorter duration of the procedure. The total duration and dosage of dexmedetomidine were probably lesser in the present study as compared to the cardiac surgical patients.[21] Secondly, the extent of myocardial damage is probably lesser in PCI patients as compared to cardiac surgical patients. The myocardial damage caused by surgical handling is more due to the duration of surgery, increased inflammation, vasopressors and surgical stress. Thirdly, the sample size was calculated based on previous surgical studies. Maybe a larger sample size was required in PCI patients. Further studies with a different dosage and/or duration with larger sample size is required to validate the myocardial protective effect in I/R injury.

CONCLUSION

Dexmedetomidine is an effective drug used for conscious sedation in anxious patients undergoing PCI.[22,23] The role of dexmedetomidine in myocardial protection of PCI patients could not be proved with respect to cardiac enzymes. However, even though dexmedetomidine decreased the coronary vessel diameter, it had also decreased the HR. Thus, the authors assume that it maintains the myocardial oxygen supply-demand ratio, leading to a myocardial protective effect.

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Conflicts of interest

There are no conflicts of interest.

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