Dexmedetomidine for Prevention of Skeletal Muscle Ischaemia-Reperfusion Injury in Patients with Chronic Limb Ischaemia Undergoing Aortobifemoral Bypass Surgery: A Prospective Double-blind Randomized Controlled Study

Abstract
Background: Dexmedetomidine is a selective α-2 agonist used for sedation. It has also been shown to have myocardial protective effect and prevent ischemia-reperfusion injury in off-pump coronary artery bypass patients. The aim of our study was to assess the effect of dexmedetomidine for prevention of skeletal muscle ischemia-reperfusion injury in patients undergoing aortobifemoral bypass surgery. Methodology: Sixty adult patients (Group dexmedetomidine n = 30, Group normal saline n = 30) undergoing aortobifemoral bypass surgery were recruited over 3 months. Randomization was done using a computer-generated random table. The attending anesthesiologist would be blinded to whether the drug/normal saline was being administered. He would consider each unlabeled syringe as containing dexmedetomidine and calculate the volume to be infused via a syringe pump accordingly. Dexmedetomidine infusion (1 mcg/kg) over 15 minutes was given as a loading dose, followed by maintenance infusion of 0.5 mcg/kg/h till 2 h postprocedure in Group dexmedetomidine (D) while the same volume of normal saline was given in the control Group C till 2 h postprocedure. Creatine phosphokinase (CPK) values were noted at baseline (T0), 6 h (T1), 12 h (T2), and 24 h (T3) after the procedure. Hemodynamic variables (heart rate [HR] and mean blood pressure [MAP]) were recorded at T0, T1, T2, and T3. Results were analyzed using unpaired Student’s t-test, P < 0.05 was considered statistically significant. Results: MAP and HR significantly decreased in Group D as compared to control group (P < 0.05). However, the decrease was never <20% of the baseline. The CPK values at 6, 12, and 24 h were statistically significant between the two groups. Conclusion: Dexmedetomidine prevents skeletal muscle ischemia-reperfusion injury in patients undergoing aortobifemoral bypass surgery.

Keywords: Aortobifemoral bypass, dexmedetomidine, ischemia-reperfusion injury

Introduction
Dexmedetomidine is a selective α-2 agonist used for sedation. Its use is increasing both inside and outside operation theaters because of its unique property of providing sedation without causing respiratory depression.[1] Dexmedetomidine has been shown to have a cardioprotective effect by attenuating ischemia-reperfusion injury in animal models.[2,3] In humans also, dexmedetomidine has been shown to have myocardial protective effect in off-pump coronary artery bypass patients.[4] The authors hypothesized that the use of dexmedetomidine in the vascular operation theatre may offer the benefit of preventing skeletal muscle ischemia-reperfusion injury in patients undergoing lower limb bypass surgeries under general anesthesia.

The aim of our study was to assess the effect of dexmedetomidine for prevention of skeletal muscle ischemia-reperfusion injury in patients undergoing vascular surgery.

Methodology
After taking Institutional Ethics Committee approval and written informed consent, sixty adult patients undergoing aortobifemoral bypass surgery for chronic limb ischemia were included over 3 months. A specific type of surgery was selected so that any bias arising due to duration of surgery, duration of cross-clamping of aorta, and site of cross-clamping may be avoided.

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All these patients underwent coronary angiography before the procedure, and patients with >30% blockage of any epicardial coronary vessel were excluded from the study.

The sample size was calculated based on a previous study keeping the value of alpha-error as 0.05 and power of the study as 90%. A minimum sample size of 30 was selected in each group, even though the sample size calculated was <30 to avoid bias of using n-1 in calculations.

All these surgeries were performed under general anesthesia. Standard drugs were used for induction of general anesthesia in all the patients, i.e., midazolam, fentanyl, propofol, and vecuronium in standard doses. Sevoflurane was used for maintenance of anesthesia and vecuronium was used for muscle relaxation. In addition, an epidural catheter was inserted in all patients at L2–L3 level for postoperative analgesia through which a continuous infusion of 0.25% bupivacaine +1 mcg/ml fentanyl was started at 4–6 ml/h at the end of the procedure.

Maintenance fluid (normal saline [NS]) was given to all patients at 1 ml/kg/h during the procedure and till the time patients were kept nil by mouth in the postoperative period.

Randomization was done using a computer-generated random table for this double-blind study. Patients were randomized into two groups:

- Group dexmedetomidine (D) (n = 30): Dexmedetomidine infusion (1 mcg/kg) was given over 15 min as a loading dose after 1/2 h of induction of anesthesia, when hemodynamics stabilized
- Group NS (n = 30): Normal saline was given in the control group after 1/2 h of induction of anesthesia.

A person not related to the study would prepare the drug in an unlabeled syringe and hand it to the duty anesthesiologist. The attending anesthesiologist would be blinded to whether the drug/NS was being administered. He/she would consider each unlabeled syringe as containing dexmedetomidine and calculate the volume to be infused via a syringe pump accordingly. Thus, in both the groups, the infusion was continued as per the protocol in all patients of either group. There was no requirement of injection dopamine in any patient.

After completion of the bolus dose, maintenance infusion of dexmedetomidine and normal saline would be administered till 2 h postprocedure in Group D and Group C, respectively, from the unlabeled syringe. As mentioned above, the attending anesthesiologist would consider each syringe to contain dexmedetomidine and administer the maintenance dose as calculated by 0.5 mcg/kg/h.

The time to extubation after shifting to recovery and the modified Ramsay Sedation Score postextubation were comparable in the two groups.

At the end of the study, the duty anesthesiologist would hand over the filled proforma to the primary investigator.

Although malondialdehyde is a more specific marker of injury, it is more expensive than CPK and is not routinely done in all institutes, including the present study institute. In addition, CPK has been used as a marker of ischemia-reperfusion injury in previous studies. Hence, it was decided to measure the levels of CPK at various time intervals as follows:

- T0 - At baseline
- T1 - At 6 h postprocedure
- T2 - At 12 h postprocedure
- T3 - At 24 h postprocedure.

Hemodynamic variables (heart rate [HR] and mean blood pressure [MAP]) were closely monitored throughout the procedure and recorded at T0, T1, T2, and T3. It was decided to stop the infusion of the unlabeled syringe if MAP decreased to <60 mmHg or HR decreased to <50 beats/min. Rescue drugs in the form of injection mephentermine in 6 mg boluses intravenously (i.v.) and injection atropine 0.6 mg i.v. were to be given for hypotension and bradycardia, respectively. In case of persistent hypotension, it was decided to start injection dopamine at 5–10 mcg/kg/min.

Results were analyzed using unpaired Student’s t-test. P < 0.05 was considered statistically significant.

**Results**

Baseline hemodynamics (MAP and HR) were comparable in the two groups [Table 1]. MAP and HR significantly decreased in Group D as compared to control group (P < 0.05). However, the decrease was never <20% of the baseline. MAP never decreased <60 mmHg and HR never decreased <50 beats/min in any patient. Hence, the unlabeled infusion was continued as per the protocol in all patients of either group. There was no requirement of injection dopamine in any patient.

The duration of surgery, duration of infrarenal cross-clamping of aorta, and time to extubation after shifting to recovery were comparable in the two groups [Table 2]. The modified Ramsay Sedation Score was higher in dexmedetomidine group than in control group at T1 and T2. But at both these time intervals, the patients were arousable to vocal commands, and at no point of time, there was a fall in SpO2 in patients receiving dexmedetomidine.

The CPK values at 6, 12, and 24 h were statistically significant between the two groups [Table 3].

**Discussion**

The prevalence of peripheral arterial disease (PAD) is expected to increase across the world as the population ages, cigarette smoking persists, and the epidemic of diabetes mellitus and obesity grows. Critical limb ischemia (CLI), defined as chronic ischemic rest pain, ulcers, or gangrene attributable to objectively
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Various mechanisms have been proposed for ischemia-reperfusion injury. Ischemia leads to a decrease in oxygen supply, which causes a depletion of ATP. This inhibits the ATP-dependent Na⁺-K⁺ pump. This leads to increase in Na⁺ levels. This further leads to increase in Ca²⁺ via Na⁺-Ca²⁺ pump. This is proposed as the molecular basis of ischemia-reperfusion injury. Secondly, there is increased free radical production upon reperfusion. Thirdly, there is a decrease in nitric oxide (NO) due to a decrease in endothelial NO synthase and increase in superoxide. Fourthly, there are increased vasoconstrictors such as endothelin I and angiotensin II. Finally, there is an increased secretion of pro-inflammatory cytokines and complement factors, which lead to increased adhesion of neutrophils. All these mechanisms have been proposed to cause ischemia-reperfusion injury.

Dexmedetomidine may act at various levels and help in decreasing the ischemia-reperfusion injury. It may have an anti-inflammatory effect by decreasing cytokines as was shown by Kang et al. Furthermore, dexmedetomidine decreases free radicals by protecting against lipid peroxidation. Dexmedetomidine has been shown to decrease oxidative stress and to strengthen the antioxidant defense system.

Dexmedetomidine has been used for the prevention of ischemia-reperfusion injury in myocardium in various studies. It has been proven to have a myocardial protective effect. However, very little literature is available for the use of dexmedetomidine for the prevention of ischemia-reperfusion injury in non-cardiac surgery settings, including its use in vascular surgery.

Hence, the authors decided to conduct the present study to evaluate the role of dexmedetomidine in one of the non-cardiac major surgical settings, i.e., in vascular surgeries.

The authors found a significant difference between the enzyme levels in patients who received dexmedetomidine and those who did not. Similar results were seen in the study conducted by Yagmurdur et al. in which dexmedetomidine offered advantage over the control group as far as CPK levels were concerned in cases of anticipated ischemia-reperfusion injury in patients undergoing upper extremity surgery with tourniquet application. The MAP and HR were significantly lower in the group receiving dexmedetomidine, although they never decreased by >20% to warrant any intervention. A similar hemodynamic response was seen in previous studies where dexmedetomidine was used for the prevention of ischemia-reperfusion injury.

Hence, dexmedetomidine provides protection against ischemia-reperfusion injury in patients undergoing vascular surgery, which may warrant its routine use in such patients.

As mentioned above, a limitation of the study was that malondialdehyde levels were not studied in the present study, even though malondialdehyde is a better marker for oxidative stress.
of skeletal muscle ischemia-reperfusion injury. However, malondialdehyde is more expensive and not routinely done in the present study institute. So, in the paucity of funds, we had to go by another easily available marker, i.e., CPK, which has also been used in previous studies.\textsuperscript{5,17}

**Conclusion**

It can be concluded that dexmedetomidine prevents skeletal muscle ischemia-reperfusion injury in patients undergoing aortobifemoral bypass surgery for chronic limb ischemia.

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Nil.

**Conflicts of interest**

There are no conflicts of interest

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