

Original Article

Intravenous dexmedetomidine and ropivacaine in lumbar plexus-sciatic and nerve blocks for tourniquet-induced ischemia-reperfusion injury in lower limb

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Abstract: Objective: To investigate the effect of dexmedetomidine on ischemia-reperfusion injury in lower-limbs in patients undergoing lower-limb orthopedic surgery who had received dexmedetomidine plus ropivacaine for a combination of lumbar-plexus and sciatic nerve-blocks anesthesia. Methods: From January 2014 to December 2016, a total of 100 patients with lower limb fracture admitted to the Department of Orthopedics in our hospital who were planned to receive lower limb fracture surgery with a combination of lumbar-plexus and sciatic-nerve blocks anesthesia were enrolled in this study. They were randomly assigned to receive a combination of lumbar-plexus and sciatic-nerve blocks anesthesia with either 50 mL of 0.5% ropivacaine alone (control group, n=50) or 50 mL of 0.5% ropivacaine plus intravenous dexmedetomidine at 1 µg/kg (intervention group, n=50). Femoral venous blood was collected from the patients at diverse time intervals (before tourniquet release (T1), at 10 min (T2), 30 min (T3), and 60 min (T4) after tourniquet release, respectively). The expression levels of superoxide dismutase (SOD), propylene glycol (MDA), TNF-α and IL-8 of patients in both groups were detected by the enzyme-linked immunosorbent assay (ELISA). Moreover, the indexes of P_aO_2 , P_aCO_2 and $P_{A-a}DO_2$ were also compared between the two groups. Results: At T2, T3, and T4 respectively, the SOD levels in the intervention group were markedly higher than those in the control group, but the MDA levels and the levels of inflammatory cytokines TNF-α and IL-8 were considerably lower (All $P < 0.05$); besides, the P_aO_2 and $P_{A-a}DO_2$ levels were also markedly higher in the intervention group at T2, T3 and T4 (All $P < 0.05$), but the P_aCO_2 levels differed mildly among the patients in both groups at any time point (T1, T2, T3, and T4; all $P > 0.05$). Conclusion: Intravenous dexmedetomidine plus ropivacaine anesthesia for combined lumbar-plexus and sciatic-nerve blocks reduce tourniquet-induced ischemia-reperfusion injury in lower limb surgery.

Keywords: Dexmedetomidine, ropivacaine, lower limb orthopedic surgery, tourniquet, ischemia-reperfusion injury

Introduction

Anesthesia of lumbar-plexus in combination with sciatic-nerve blocks is a common method of lower limb anesthesia, and ropivacaine is a conventional anesthetics used in clinical operation. Recently, as the lower limb surgery is increasingly complex and longer, the clinical anesthetics have been constantly updated. On the basis of analgesia, the patient is also required to be relatively static, especially in case of recurrent long-term compression of the tourniquet. The patient is prone to have massive hemorrhage due to the rich blood supply in the lower extremities during the intraoperative period. The tourniquet, advantageous in

reducing intraoperative blood loss and maintaining clear vision of the surgery, has been extensively used in limb surgeries [1, 2]. However, inflated tourniquets might lead to reduced limb blood supply, and ischemia in tissues; deflated tourniquets might give rise to ischemia-reperfusion injury and secondary oxidative stress and inflammation, which not only aggravates the injury induced by the primary diseases, but also makes damage to other organs [3, 4].

Dexmedetomidine, a highly selective α_2 receptor agonist, has the functions of sedation, analgesia, sympathetic nerve block and anti-anxiety [5, 6]. Several studies have shown that proper

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amount of dexmedetomidine combined with local anesthetics is effective in intra-vertebral anesthesia or peripheral nerve block [7, 8]. According to another study, dexmedetomidine reduced oxidative stress and inflammatory response by regulating the immune function, thereby reducing the ischemia-reperfusion injury to the organs [9]. Currently, the protective function of dexmedetomidine to the ischemia-reperfusion injury induced by tourniquet remains unclear. The purpose of the present study was to explore the effects of dexmedetomidine on ischemia-reperfusion injury in lower-limbs in patients undergoing lower-limb orthopedic surgery who had received dexmedetomidine plus ropivacaine for anesthesia with lumbar-plexus combined with sciatic-nerve blocks, so as to bring insight into future clinical practice.

Materials and methods

Participants

This study met the requirements of the Hospital Ethics Committee, and each of the patients was asked to provide written informed consent. Between January 2014 and December 2016, 100 patients undergoing lower limb fracture surgery in the Department of Orthopedics in our hospital were selected as participants. There were 65 males, 35 females, with a mean age of 36.4 ± 5.2 years, a mean body mass index (BMI) of 24.1 ± 2.1 kg/m², and the American Society of anesthesiologists (ASA) Grade of I-II. Patients over 18 years old were eligible for this study if they were in requirements of long-time application of tourniquets for the surgery and had operation under anesthesia with lumbar plexus combined with sciatic nerve blocks. Patients were excluded if they had severe organ dysfunction, injection-site infection, local anesthetics allergy, diabetes mellitus, rheumatic autoimmune disease, mental disorder or infectious disease. The patients were randomly assigned to undergo anesthesia with lumbar-plexus combined with sciatic-nerve blocks with either 50 mL of 0.5% ropivacaine alone (control group, n=50) or 50 mL of 0.5% ropivacaine added to intravenous dexmedetomidine at 1 µg/kg (intervention group, n=50).

Methods

For all the patients, routine food and water fasting were required before surgery, and oxygen

inhalation and electrocardiographic (ECG) monitoring were performed after they were in the operation room. With the stimulation frequency set at 2 Hz and the initial current at 2 mA, the positive electrode plate of the nerve stimulator was placed adjacent to the thigh skin of the patient and the stimulation needle was connected with the negative electrode.

The control group received ropivacaine anesthesia, and the intervention group was given with ropivacaine and dexmedetomidine anesthesia. Dexmedetomidine was administered intravenously at 1 µg/kg.

Lumbar-plexus block anesthesia: After routine skin disinfection, the patients were placed in a lateral decubitus position with knee flexion and the affected lower limb up. The puncture point was at the site 5 cm above the intersection between the line linking the uppermost points of the iliac crests and the spinous process. A needle was advanced slowly and vertically through the skin, followed by spasm of quadriceps femoris. The current dropped to 0.3 mA, when there was still mild motor response of the quadriceps femoris group. Slow bolus infusion of anesthetic drugs (30 ml) was performed when no cerebrospinal fluid and blood were pumped back.

Sciatic-nerve block anesthesia: After routine skin disinfection, the patients were placed in the lateral decubitus position. With the hip joint flexing upward 30 degrees and the knee joint flexing upward 90 degrees, the puncture point was at the site 5 cm above the vertical line intersecting the midpoint of the line linking the posterior superior iliac spine to the greater trochanter of the femur. A needle was advanced slowly, followed by spasm of gastrocnemius muscle. The current dropped to 0.3 mA, when there was still muscular fibrillation. Slow bolus infusion of anesthetic drug (20 ml) was performed when no cerebrospinal fluid and blood were pumped back. The tourniquet was stabilized at the one-third upper of the thigh, and the pressure parameter was set with a rise of 100 mmHg in preoperative systolic pressure. The tourniquet was released for 10 min after 60 min of tourniquet use during the intraoperative period.

Measure outcomes

Femoral blood samples (5 ml) were drawn from each patient before tourniquet use (T1), at 10

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Table 1. Comparison of general clinical data between the two groups

Variable	Case	Male/Female (n)	Age (year)	BMI (kg/m ²)	Tourniquet use (min)	Tourniquet pressure (mmHg)	ASA grade (n)	
							I	II
Intervention group	50	32/18	35.2±4.9	23.6±1.9	85.4±8.9	225.7±15.8	27	23
Control group	50	33/17	37.6±5.5	24.6±2.3	83.8±8.4	222.9±15.1	25	25
t/χ ²		2.775	2.538	2.472	2.632	2.842	1.032	
P		0.417	0.482	0.491	0.456	0.389	0.779	

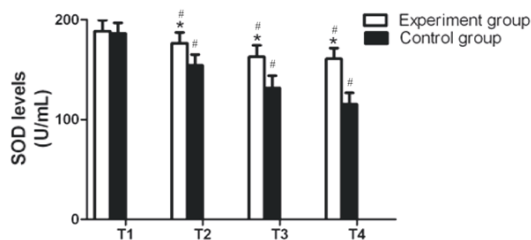


Figure 1. Comparison of SOD levels between the two groups at different time points. Compared with the control group at the same time point; *P=0.000; compared within the same group at T1, #P=0.000.

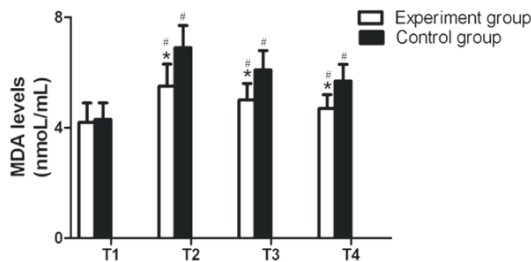


Figure 2. Comparison of MDA levels of patients between the two groups. Compared with the control group, *P=0.000; compared within the same group at T1, #P=0.000.

min (T2), 30 min (T3) and 60 min (T4) after tourniquet release, respectively. The blood samples were centrifuged for 10 min at 3000 r/min, from which the supernatant was extracted and stored in an aseptic tube at -20°C. The levels of TNF-α, IL-8, propylene glycol (MDA) and superoxide dismutase (SOD) were detected by the enzyme-linked immunosorbent assay (ELISA). The arterial blood gases of the two groups were detected at different time points, and the P_aO₂, P_aCO₂ and P_{A-a}DO₂ indexes were compared between the two groups.

Statistical analysis

All the data were analyzed using the SPSS software, version 20.0. Measurement data were represented as mean ± sd; the t-test was utilized for between-group comparison whereas

the repeated measures analysis of variance was used for comparisons at diverse time points. Count data was expressed as percentages and the chi square test was applied for between-group comparison. P values of less than 0.05 were set to be of statistical significance.

Results

General data

Among the patients in the intervention group, there were 32 males and 18 females. They had a mean age of 35.2±4.9 years, a mean mass index (BMI) of 23.6±1.9 kg/m², an average time for tourniquet use of 85.4±8.9 min and an average tourniquet pressure of 225.7±15.8 mmHg. ASA Grade I occurred in 27 patients and ASA Grade II in 23. Among the patients in the control group, 33 patients were male and 17 were female. They had a mean age of 37.6±5.5 years, a mean BMI of 24.6±2.3 kg/m², the mean tourniquet use of 83.8±8.4 min and a mean tourniquet pressure of 222.9±15.1 mmHg. ASA Grade I occurred in 25 patients and ASA Grade II in 25. No statistically significant differences were noted in age, gender, BMI, time for tourniquet use and tourniquet pressure between the two groups (P>0.05, **Table 1**).

SOD levels

At T1, no noticeable difference was observed in SOD levels between the two groups (P>0.05). The SOD levels at T2, T3, and T4 respectively were strikingly higher in the intervention group than in the control group (P=0.000). The SOD level of all the patients at T2, T3, and T4 respectively were substantially lower than that at T1 (All P=0.000, **Figure 1**).

MDA levels

The MDA levels at T1 differed insignificantly between the two groups (P>0.05). The MDA lev-

Table 2. Comparison of TNF- α and IL-8 levels between two groups

Variable	Group		t value	P value
	Intervention	Control		
Case	50	50		
TNF- α (pg/mL)				
T1	2.5 \pm 0.7	2.6 \pm 0.8	1.659	0.623
T2	5.6 \pm 1.3* [#]	7.9 \pm 1.7 [#]	16.394	0.002
T3	5.7 \pm 1.4* [#]	7.7 \pm 1.5 [#]	15.384	0.006
T4	5.4 \pm 1.2* [#]	7.5 \pm 1.3 [#]	14.027	0.025
IL-8 (pg/mL)				
T1	113.2 \pm 11.2	112.8 \pm 10.8	1.517	0.692
T2	134.5 \pm 12.4* [#]	159.7 \pm 13.3 [#]	14.266	0.019
T3	131.7 \pm 11.9* [#]	154.2 \pm 12.1 [#]	13.955	0.032
T4	129.6 \pm 10.6* [#]	149.9 \pm 11.5 [#]	14.261	0.014

Note: Compared with the control group, *P<0.05; Compared within the same group at T1, [#]P=0.000.

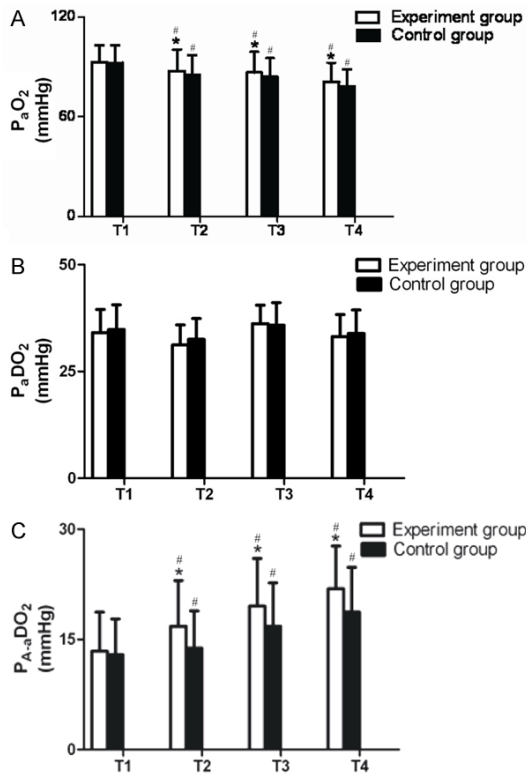


Figure 3. Comparison of P_aO_2 , P_aCO_2 , and $P_{A-a}DO_2$ levels at diverse time points between the two groups. Compared with the control group, *P=0.000; Compared within the same group at T1, [#]P=0.000.

els at T2, T3, and T4 respectively were substantially lower in the intervention group than in the control group (All P=0.000, **Figure 2**). The MDA level of all the patients at T2, T3 and T4 respec-

tively were substantially higher than that at T1 (All P=0.000).

Inflammatory cytokine levels

No striking difference between the two groups was noted in the TNF- α and IL-8 levels before tourniquet use (Both P>0.05). The levels of TNF- α and IL-8 in the intervention group were noticeably lower than those in the control group at T2, T3 and T4, respectively (All P=0.000). The levels of TNF- α and IL-8 of both groups at T2, T3, and T4 were considerably higher than that at T1 (All P=0.000, **Table 2**).

P_aO_2 , P_aCO_2 , and $P_{A-a}DO_2$ levels

The P_aO_2 , P_aCO_2 , and $P_{A-a}DO_2$ levels at T1 were different mildly between the two groups (All P>0.05). At T2, T3, and T4 respectively, the P_aO_2 and $P_{A-a}DO_2$ levels were markedly higher in the intervention group versus in the control group (Both P<0.05), but the P_aCO_2 levels differed insignificantly between the two groups (P>0.05); Among the patients in both groups, the P_aO_2 levels at T2, T3, and T4 respectively were lower than that at T1, but the $P_{A-a}DO_2$ levels at T2, T3, and T4 respectively were substantially higher than that at T1 (All P=0.000, **Figure 3**).

Discussion

Normal metabolism of the tissues lies in good blood circulation. However, various factors may lead to local ischemia in tissues, which causes ischemic injury in tissues. Reperfusion under certain conditions exacerbates damages to metabolic function or structure in cells and tissues, the phenomenon of exacerbation of ischemic injury following blood perfusion is defined as ischemia reperfusion injury [10-12]. Tourniquet is extensively used for limb surgeries. Although tourniquet allows longer operation and clearer vision, the tourniquet-induced ischemia reperfusion injury has attracted much attention from clinicians.

After tourniquet use following lower limb orthopedic surgery, the lower limbs are ischemic, where a sea of hypoxia metabolites including OH, O_2^- , and H_2O_2 aggregate. After tourniquet release, the blood supply restores in the limbs.

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A large number of oxygen radicals produce peroxides by interacting with unsaturated fatty acids on cell membrane, causing damages to cells and mitochondria; the peroxides become unstable and are further degraded to MDA, leading to damages to the distal organs with the ongoing blood circulation [13, 14]. SOD has shown to be the most important antioxidant active substance in the organism as it effectively scavenges oxygen radicals [15, 16]. The results of the current study showed that at different time points of T2, T3 or T4, the SOD levels were significantly higher, but the MDA levels were strikingly lower in the intervention group when compared to the control group, suggesting that dexmedetomidine can reduce damage to oxidative stress caused by tourniquet-induced ischemia-reperfusion injury. This is basically consistent with the reports in previous studies worldwide [17, 18].

Inflammation is another key mechanism of tourniquet-induced ischemia-reperfusion injury, oxidative stress tends to be accompanied by inflammation, and then the inflammatory cascade reaction is caused by the release of many inflammatory mediators in the blood exacerbates the ischemia reperfusion injury. According to one study, TNF- α , one of the most sensitive and the earliest inflammatory mediators in the development of ischemia reperfusion injury, may result in damaged vascular endothelial cells, increased vascular permeability, and better release of other inflammatory mediators [19]. In another study, IL-8 was reported to be bound to specific receptors on the surface of neutrophils to form large amounts of oxygen radicals, which damaged the organs and tissues of the organism [20]. The results of the current study indicated that the levels of TNF- α and IL-8 in the intervention group were noticeably lower than those in the control group at the different time points of T2, T3 and T4, respectively. These results indicate that dexmedetomidine can reduce the damage to organ tissues in the course of the tourniquet-induced ischemia-reperfusion injury. In addition, the lung, owing to its high perfusion, large external contact area and sensitivity to inflammatory mediators, is the organ where tourniquet-induced ischemia reperfusion injury is most likely to be involved in. The severe injury may develop into acute lung injury, even acute respiratory distress syndrome. In the current study, at T2,

T3, and T4 respectively, the P_aO_2 and $P_{A-a}DO_2$ levels in the intervention group were strikingly higher than those in the control group. P_aO_2 is a predictor of pulmonary ventilation function, while $P_{A-a}DO_2$ is a predictor of pulmonary gas exchange. Therefore, dexmedetomidine can protect the distal lung from ischemia-reperfusion injury induced by tourniquet in lower limb orthopedic surgery.

In conclusion, dexmedetomidine relieved ischemia-reperfusion injury induced by tourniquet in lower limb orthopedic surgery under lumbar plexus-sciatic nerve block anesthesia. It is worth of extensively clinical use. The limitations in the current study included no exploration of limb local ischemia in patients, no multi-dose study of dexmedetomidine, no research in specific mechanism, as well as a small sample size. All the above aspects are needed to further elucidation in the future studies.

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Disclosure of conflict of interest

None.

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