Original Article

Remote Ischemic Preconditioning in Lower Limb Surgery; the Hemodynamic and Respiratory Effects

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Abstract

Background: Remote Ischemic Preconditioning introduces brief episodes of ischemia and reperfusion, which reduces long term ischemia in orthopedic surgery. The aim of this study was to evaluate hemodynamic and respiratory effects of remote ischemic preconditioning in lower extremity orthopedic surgeries.

Materials and Methods: In this clinical trial, 40 patients scheduled for lower extremity surgery with pneumatic tourniquet were randomly allocated to remote ischemic preconditioning (RIP) group (n=20) and the control group (n=19). Patients in RIP group received three "5 minutes" cycles of ischemia, alternating with 5 minutes of reperfusion before extending the use of tourniquet. Hemodynamic variables prior to inflation of tourniquet, every 30 minutes during the surgery and 10 minutes after tourniquet deflation and also arterial blood gas sample prior to and after surgery were recorded and compared between groups.

Results: During operation blood pressure dropped in the RIP group and variations in heart rate, respiratory rate, and pulse oximeter measurements after surgical tourniquet release were not significantly different between two groups. Changes in blood gas parameters were significantly less pronounced in the RIP group.

Conclusion: Remote ischemic preconditioning may not attenuate most of the adverse effects of surgical tourniquet deflation, including variations in heart rate, respiratory rate, and arterial oxygen saturation as well as blood pressure drops. However, RIP may reduce increases in systolic blood pressure and acidosis following tourniquet application.

Keywords: Remote Ischemic Preconditioning, Orthopedic, surgery, blood pressure, tourniquet, oxygenation

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Introduction

Use of tourniquets in orthopedic surgery improves the quality of the surgical field and reduces intraoperative bleeding (1). However, tourniquet application leads to disadvantages and complications (2). The local and systemic effect of tourniquet is due to direct compression and ischemia caused in the area

which the tourniquet is applied. Systolic and diastolic rise in blood pressure (BP), increase in heart rate (HR) and respiratory rate (RR), secondary brain injuries due to increased intracranial pressure, release and secretion of inflammatory and pain mediators, body temperature rise, the increase in serum lactate and potassium levels and regional damage caused by cuff pressure are some of the potential physiological and hemodynamic complication of tourniquet application (3).

Remote Ischemic Preconditioning (RIP) is defined as short episodes of ischemia-reperfusion, which protects an organ or limb against the adverse effects of prolonged duration of ischemia. Although the underlying mechanism of this protection is not completely understood, different hormonal and neurological pathways have been proposed as the mechanism. In cardiac surgery, RIP reduces the use of inotropes, the incidence of cardiac arrhythmias and hospital stay in the intensive care unit (4). Similar studies have demonstrated that the effect of tourniquet on cardiac protection and reduction of myocardial injury biomarkers (5, 6). Other studies have suggested that RIP may reduce the impairment in pulmonary gas exchange and fat peroxidation following the tourniquet application in patients undergoing lower limb fracture surgeries (7). However, the findings of earlier studies are conflicting (7-9). We conducted this randomized, double blind clinical trial to investigate the hemodynamic and respiratory effects of RIP in patients with isolated lower limb fracture surgery.

Methods

Study population

Forty patients with ASA physical status I–III candidate for elective isolated lower limb orthopedic surgery were enrolled. Exclusion criteria included those with other limb fracture, need for more than 1 mg midazolam for sedation, failure of spinal anesthesia, tourniquet application for less than 1 hour, history of drug abuse and the need for intraoperative blood pressure (BP) lowering agents. Informed consent was obtained from all participants before surgery. Approval from the local Ethics Committee was obtained. The study was registered in the Iranian register clinical trial center by IRCT201304055026N2 number.

Study Design

Patients were randomly allocated to the RIP (n=20) and the control group (n=20) using block randomization. To randomize patients into two groups random number table was used to allocate 10 blocks. The sequence was stored in concealed envelopes from number 1 to 40. Patients, anesthesiologist and the statistician were blinded to the assignments. In order to facilitate blind, a second cuff was applied on the other limb of control patients while deflated.

All patients received midazolam (1mg IV) for sedation and underwent spinal anesthesia in the sitting position with a Whitacre needle 25 Gauge at L3-L4 interspace. After clear CSF flow, 10-15 mg Bupivacaine 0.5% considering the patient's weight and height was injected. Level of spinal anesthesia was considered up to T6. Sensory and motor block was recorded by a blind investigator. Preconditioning was performed with three intermittent 5-minute cycles of ischemia using a tourniquet inflated 100 mmHg above the patients' baseline systolic blood pressure (sBP) (ischemia period). Between ischemic periods, the tourniquet was deflated for 5 minutes, allowing reperfusion (Reperfusion period). The patients in the control group were observed for 25 minutes with the control cuff maintained deflated.

Measurements

Demographic and hemodynamic data (systolic and diastolic blood pressure (sBP and dBP), heart rate (HR), respiratory rate, and arterial blood oxygen saturation) for all patients were recorded at baseline and every 30 minutes after tourniquet application as well as 10 minutes after its deflation. Blood pressure measurements were conducted by a standard sphygmomanometer, heart rate with electro cardiac monitoring and pulse oximeter with the application of the standard monitoring system (Alborz Model 25, Saadat Company). Blood sugar was measured with glucometer (Lever check, made in Taiwan). Time of tourniquet inflation, duration of surgery, intraoperative blood loss and fluid therapy were recorded for all patients. Arterial line was inserted for all patients using local anesthetics and blood samples were obtained for gas analysis immediately before surgical tourniquet deflation and one min thereafter.

Statistical Analysis

Student's t-test was used to examine differences between continuous variables (blood pressure, pulse rate, oxygen saturation, and respiratory rate) and Chi square for categorical variables. The trend of BP and HR between groups was compared with repeated measurements of ANOVA. P values less than 0.05 were considered as statistically significant. The Statistical Package for Social Science (SPSS) for Windows, version 12.0 (Chicago, IL, USA) was used for all analysis.

Results

Demographic data, duration of surgery, baseline laboratory measurements, intraoperative blood loss and fluid therapy were comparable between two groups (Table 1). Systolic BP gradually increased during the application of a surgical tourniquet in the control group, whereas RIP significantly blunted this increase (Figure 1). The trend of dBP, HR and the spontaneous respiratory rate were similar between two groups (Data not shown).

Blood pressure drops and variations in heart rate, respiratory rate and pulse oximeter measurements after surgical tourniquet release were not significantly different between two groups (Table 2). Blood pressures gained baseline levels 10 minutes after deflation.

Blood gas analysis showed that tourniquet deflation after a prolonged ischemic period result in acidosis. Changes in blood gas parameters were significantly less pronounced in the RIP group (Table 2).

Discussion

The findings of this study suggest that RIP may reduce the severity of tourniquet-induced hypertension and acidosis. However, it may not provide extra benefits for the maintenance of respiratory and hemodynamic stability after tourniquet deflation. The results of similar earlier studies are conflicting, ranging from no clinical benefit (7-10) to protection against BP

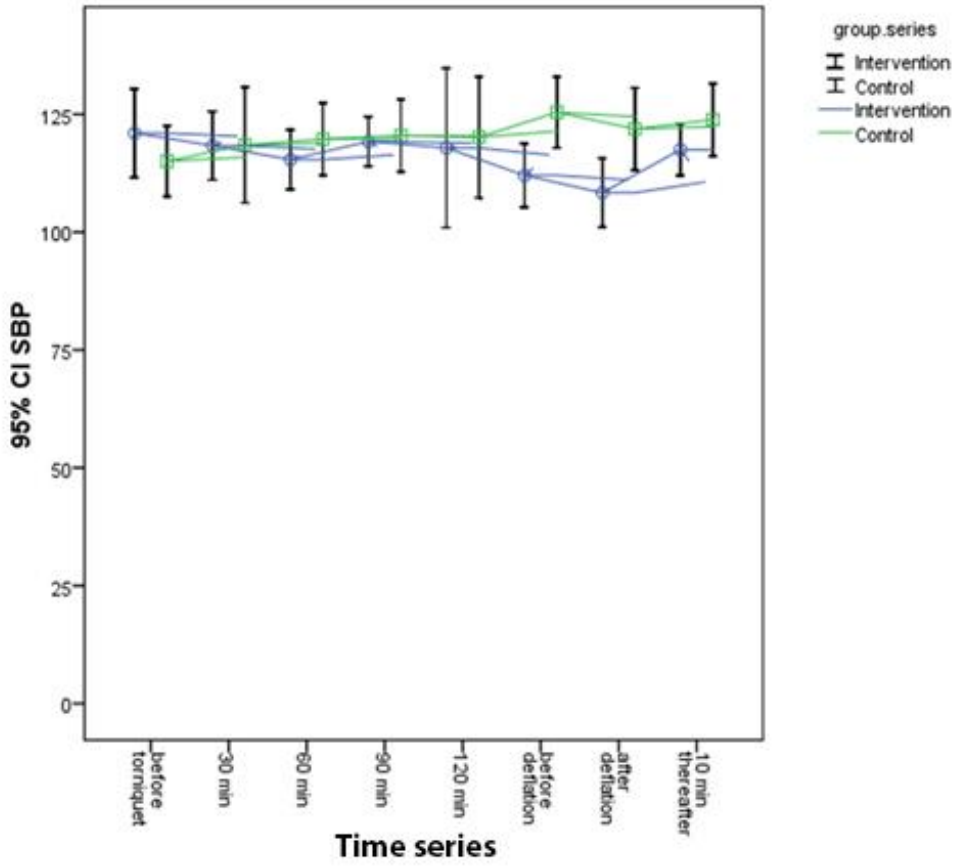

Fig. 1. The trend of mean systolic blood pressure with interpolation lines**.**

Table 1: Demographic data and intraoperative measurements.

		RIP(n=20)	Control(n=20)	P value
Age (y)		53	43	≥0.05
Gender(M/F)		12/8	16/4	0.09
Tourniquet time(min)		108.35(23.24)	105.53(27.73%)	0.7
Surgery Time(min)		128.75(30.43)	127.47(34.1%)	0.9
Bleeding (cc)		149.6(97.05)	170(116.09%)	0.5
Serum therapy(lit)		1.86(0.55)	1.61(0.55%)	0.1
Blood Sugar(mg/dl)		103(17.55)	95.79(20.13%)	0.2
ASA	**I**	8(40.0%)	11(55.0%)	19(51.4%)
	II	19(51.4%)	19(51.4%)	19(51.4%)
	III	1(5.0%)	1(5.0%)	2(5.4%)

ASA: American society of anesthesiologists
Data presented as mean (SD)

drops and tachypnea after surgical tourniquet deflation (23).

Remote ischemic preconditioning confers protection in skeletal muscles and body organs to

Table 2: Blood gas values, hemodynamic and respiratory measurements before and after surgical tourniquet deflation.

	RIP(n=20)			Control(n=20)		
	Before	**After**	**P value**	**Before**	**P value**	**After**
PH	7.38(0.05)	7.36(0.05)	0.3	7.4(0.06)	7.37(0.04)	0.02
Pco2	38.9(5.19)	39.2(5.75)	0.6	38.4(5.56)	40.1(5.93)	0.03
HCo3	22.94(3.25)	23.46(2.64)	0.4	24.1(2.93)	22.87(2.34)	0.009
Systolic BP	112(14)	108(15)	≥0.05	125(16)	121(18)	≥0.05
Diastolic BP	71(8)	66(9)	≥0.05	76(12)	71(10)	≥0.05
Heart rate	81(12)	84(11)	≥0.05	80(13)	85(16)	≥0.05
Respiratory rate	15.3(3.4)	17(4.5)	≥0.05	15.4(4)	15.4(2.9)	≥0.05
SpO_2	96%(2.5)	95.9%(2.2)	≥0.05	95.5%(5.8)	96.1%(4.8)	≥0.05

Data presented as mean (SD)

improve ischemic tolerance and thereby reduce the damage caused by long term ischemia. This clinical benefit of this phenomenon for heart, skeletal muscles, kidney, liver, intestine and lungs has been proposed earlier (17-23). However, the exact underlying mechanism is not yet clear. Stress induced cytokines, role of adenosine and ATP dependent potassium channels and neural pathways have been proposed as the possible protective mechanisms (24-26).

Hemodynamic instability is one of the complications of inflation and deflation of surgical tourniquet. Inflating the tourniquet increases blood circulation and systemic vascular resistance, thus causing a sustained increase in central venous pressure and sBP. About 30 minutes after inflating the tourniquet HR, sBP, and dBP increase, which remains high up to the deflation time (tourniquet pain phenomenon) (10). Deflating the tourniquet results in BP drops is a result of decreased vascular resistance and vascular return of the ischemic organ to the circulatory system (16,26). Similarly, in our study significant changes in BP was seen after tourniquet release in the RIP group. Immediately after tourniquet deflation modest degrees of decrease in BP were seen as a result of additional vascular return of the ischemic organ to the circulatory system. However, shortly after complete deflation BP returned to the baseline levels.

Remote ischemic preconditioning protects the lung and improves oxygenation by reducing inflammatory cytokines. Limb ischemia results in cytokines like TNF-α, IL6, and IL1β release which causes lung injury. Deflating the tourniquet results was increased arterial Co_2 content in the first minute and gains normal levels after a few minutes (11). The patients compensate this condition with an increase in respiratory rate (27-29). Similarly, in our study the patient's respiratory rate, increased after deflating the tourniquet and returned to the baseline levels within 10 minutes. In spite of higher arterial CO_2 content in control patients, clinical parameters such as respiratory rate were comparable between two groups.

The use of remote ischemic preconditioning increases the limb blood flow after a short time and prepares the tissue for long periods of ischemia. Due to anaerobic metabolism during the inflation time cellular hypoxia, hypercarbia, and acidosis evolves. Tourniquet deflation causes oxidative stress, which leads to cell membrane destruction and a rise in lactate levels. Previous studies showed that the most common metabolic change 1-2 hours after ischemia is increased lactate and potassium levels, which gains normal levels 30 minutes after opening the tourniquet (30,31). In the blood gas analysis of our patients, PH and bicarbonate levels were more profoundly decreased in the control candidates rather than the RIP group.

One limitation of this study was lack of postoperative follow-up. It would be possible that the minute adverse effects of ischemia and reperfusion would be unclosed within follow-up periods. We could not measure novel markers of reperfusion injury, such as interleukins and inflammatory factors. This limitation besides small variations in hemodynamic, respiratory and metabolic variables in our patients might influence the clinical effects of RIP to become palpable.

Conclusion

Remote ischemic preconditioning may not attenuate most of the adverse effects of surgical tourniquet deflation including variations in heart rate, respiratory rate and arterial oxygen saturation as well as blood pressure drops. However, RIP may reduce increases in systolic blood pressure and acidosis following tourniquet application. Further possible benefits of RIP on respiratory function and stress response of patients should be evaluated in future clinical trials.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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