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The Effect of Infraclavicular Block on Tourniquet-Induced Ischaemia Reperfusion Injury: A Prospective Randomized Controlled Study

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Abstract

BACKGROUND/AIMS: Ischemia-reperfusion injury (IRI) occurs due to the release of free oxygen radicals after tourniquet usage. Following tourniquet application, parameters such as ischemia modified albumin (IMA), total antioxidant status (TAS) and total oxidant status (TOS) become more frequently studied in order to reveal IRI. The aim of this study was to compare the effects of both infraclavicular block (ICB) and general anaesthesia (GA) on IRI in a prospective randomized controlled manner.

MATERIALS AND METHODS: Sixty patients undergoing extremity surgery with tourniquet were randomized in two groups (the ICB group ICB and the GA group GA). In the group ICB, anaesthesia using USG linear probe was applied via a lateral-sagittal technique. Conversely, anaesthesia was inducted with propofol and was maintained with 2-3% sevoflurane, 50% O_2/air mixture in the group GA. Blood samples were drawn before ICB and the induction of GA (T1), and again 2 hours after tourniquet opening (T2). Serum TAS, TOS and IMA levels were calculated using diagnostic kits.

RESULTS: A total 47 patients were evaluated in both groups. There was no statistical significance within or between the two groups in terms of their IMA, TAS and TOS values at T1 and T2 ($p>0.05$). In addition, there was no statistical significance within or between either group in terms of IMA, TAS and TOS values according to their tourniquet times (0-60 and 61-120 min) ($p>0.05$).

CONCLUSION: Infraclavicular nerve block and GA were not superior to each other in preventing IRI associated with a tourniquet duration of up to 120 min.

Keywords: Tourniquet, ischemia-reperfusion injury, general anaesthesia, infraclavicular nerve block

INTRODUCTION

Tourniquets are commonly used in the proximal region for limb operations to control bleeding in orthopaedic surgery. A tourniquet can cause ischemic-reperfusion injury (IRI) when applied in extremity surgery, cardiac surgery, thromboembolic events, revascularization, organ transplantation, and ischaemia restoration-induced severe hypotension and hypovolemic shock.[1] Anaerobic glycolysis is induced during ischaemia, followed by the release of pro- and anti-inflammatory cytokines, polymorphonuclear neutrophil activation and reperfusion. Simultaneously, platelet adhesion to the vascular endothelium occurs due to the production of reactive oxygen species (ROS) and the release of vasoactive factors. These free oxygen radicals trigger enzymatic

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reactions, such as the peroxidation of polyunsaturated fatty acids or plasma lipoproteins, leading to the oxidative destruction of cell membranes, the production of toxic reactive metabolites and damage to the structure of DNA, proteins and lipids.[2] The production of free radicals causes hypoxia, acidosis, sodium-calcium pump disturbance and tissue damage, leading to increased ischaemia-modified albumin (IMA) production.[3] Total antioxidant status (TAS), an indicator of antioxidant activity, counteracts oxidative stress and reperfusion damage. The production of ROS increases, whereas TAS decreases as a result of oxidative stress. Total oxidant status (TOS) is related to ROS production.[4]

During elective orthopaedic surgery, tourniquet-induced skeletal muscle ischaemia results in the oxidation of muscle proteins.[5] However, tourniquet-induced ischaemia and its immediate effects on human skeletal muscle cells have rarely been documented.[6] In this study, we investigated the effects of infraclavicular block (ICB) on tourniquet-induced ischaemia reperfusion upper extremity injury in a prospective study. These parameters were also compared between whole groups according to different tourniquet times during surgery (0-60 and 61-120 min).

MATERIALS AND METHODS

Study Group

This study was approved by the Ethics Committee of Selçuk University Faculty of Medicine (approval number: 07.03.2018/2018/05), and all the patients provided informed consent. The study group comprised 60 males and females, aged between 18 and 65 years with American Society of Anesthesiologists (ASA) physical status 3-3 undergoing routine upper extremity surgery with a pneumatic tourniquet. The exclusion criteria were as follows: cardiac, metabolic, renal, or hepatic diseases; systemic rheumatological diseases; inflammatory, autoimmune, or peripheral vascular diseases; symptomatic diabetic microangiopathy (diabetic foot, diabetic retinopathy, etc.); known limb ischaemia; deep vein thrombosis; or hemodynamic instability. Additional exclusion criteria were a history of cancer, a history of coronary artery disease within the previous year or extremity surgery within the previous 3 months, drug use which could impair acid-base balance, steroid drug use, alcohol consumption and smoking.

Sample Size Calculation and Group Allocation

The sample size in each group was determined according to the method of Omür et al.[7] According to a power analysis, to achieve a power of 0.830 and a significance of p=0.05, 22 patients were required in each group. However, to take into account possible data loss, a minimum of 30 patients were required per group.

The patients were given the choice of ICB or general anaesthesia (GA). Patient recruitment continued until there were 30 patients in each group. On reaching the required patient number (n=30) in one group, the patient were not enrolled into the other group, as the patient's choice of anaesthesia method was directed by the group allocation.

Anaesthesia Induction

The patients were taken to the operating room without any premedication. On arrival in the operating room, each patient was monitored using a standard electrocardiogram and pulse oximetry, capnography, respiratory rate and non-invasive arterial pressure measurements. Immediately prior to anaesthesia, all the patients received 0.9% sodium chloride solution administered via intravenous infusion.

Infraclavicular Block Group

Each patient in the ICB group was placed in a supine position, with the patient's head turned to the opposite side of the block. The skin over the interscalene block area was sterilized with 10% povidone iodine. The block was applied using a My Lab 30 USG (Esaote, Florence, Italy) multi-frequency linear probe (10-18 MHz). The USG linear probe was applied using a lateral-sagittal technique, when applying ICB. A 100 mm 22-G nerve stimulation needle relative to the artery in the USG image was directed at 3-6-9 clockwise. The position of the needle with the neurostimulator was confirmed by observing rhythmic contraction movements of the hand and wrist. Then, 10 mL of 2% prilocaine and 10 mL of 0.5% bupivacaine (total dose=20 mL) were given as an intermittent negative aspiration as a local anaesthetic mixture. The U-shaped spread of local anaesthesia around the three branches of the brachial plexus was confirmed by ultrasound.

General Anaesthesia Group

In the GA group, the patients were anesthetized with 2 mg/kg of propofol, 2 mg/kg of fentanyl and 0.6 mg/kg of rocuronium at the beginning of GA induction. The patients were intubated after 2 min of muscle relaxation. Anaesthesia was maintained by administering 2-3% sevoflurane, 50% O_2/air and 0.1 mg/kg/dk remifentanil infusion. At the end of the operation, the return of spontaneous breathing was provided with sugammadex (4 mg/kg), and the patients were extubated.

Data Collection and Measurements

Blood samples were drawn before ICB and the induction of GA, and these values were accepted as T1 values before tourniquet application. A pneumatic tourniquet routinely used in upper extremity procedures was inflated just before surgery to maintain the patient's mean systolic blood pressure above 100 mmHg. Blood samples were drawn again 2 hours after tourniquet opening, and these values were accepted as T1 values too. The blood samples were collected in ependurach tubes and stored at -20 °C. Serum IMA levels were measured spectrophotometrically using a spectrophotometer (Lambda, PerkinElmer, Massachusetts, USA) and the albumin-cobalt binding method. The results were recorded in absorbance units. Colorimetric method kits were used for the measurement of serum TAS and TOS levels. TAS and TOS levels were calculated (μmol H_2O_2 equivalent/L) using commercially available diagnostic kits. The TAS, TOS and IMA levels in the groups were also measured at different tourniquet times: 0-60 min and 61-120 min.

In both groups, intravenous ephedrine (5-10 mg) was administered if the systolic blood pressure decreased by more than 30% as compared with the baseline value. Atropine was administered when the patient's heart rate decreased below 50 beats/min.

Statistical Analysis

Statistical analysis of the data was performed using SPSS 21.0 (Statistical Program for Social Sciences, Chicago, IL, USA). The Kolmogorov-Smirnov test was performed to determine the normality of the data distribution. A t-test was used for comparisons of data with a normal distribution, and the non-parametric Mann-Whitney U test was used for data without a normal distribution. Demographic data and descriptive statistics of

continuous variables are presented as mean ± standard deviation. A chi-squared test was used to evaluate categorical data. A t-test was applied for between-group comparisons of measurements. A repeated measures analysis of variance was used to examine whether intra-group comparisons (T1 vs T2) showed a significant change, and a paired t-test was used for within-group comparisons. A Bonferroni correction was performed for evaluations of repeated measurements within groups. A value of $p<0.05$ was considered statistically significant.

RESULTS

In total, 60 patients were included in this study. In the ICB group, blood samples from four patients were not available because of deteriorated blood samples and/or changes in the anaesthesia method from block to GA due to the patients' pain. In the GA group, some samples were not available to use because of deteriorated blood samples and/or prolonged operation times. Thus, in the final analysis, 26 patients were included in the ICB group, and 28 patients were included in the GA group. Detailed information on the enrolment of the patients into this study is shown in the CONSORT flow diagram in Figure 1. When the demographic and clinical results of the patients were evaluated, there were no between-group differences in terms of age, gender, body mass index, ASA status, operation time, anaesthesia time or tourniquet time (Table 1). There was no statistical significance within or between the two groups in terms of TAS, TOS and IMA values at T1 and T2 ($p>0.05$) (Table 2). In addition, there was no statistical significance within or between the both groups in terms of their TAS, TOS and IMA values according to their tourniquet times (0-60 and 61-120 min) ($p>0.05$) (Table 3).

DISCUSSION

In our study, neither ICB nor GA was superior in terms of the prevention of IRI associated with tourniquet use, as determined by measurements of IMA, TAS and TOS levels in serum samples at different tourniquet times (0-60 min and 61-120 min).

The use of a tourniquet in extremity surgery can result in the temporary occlusion of blood flow and ischaemia, which causes rapid damage to metabolically active tissues. Paradoxically, restoration of blood flow (reperfusion) is associated with the generation of ROS, which damage cellular components. Various methods have been proposed to reduce tourniquet-induced IRI. Such methods include ischemic preconditioning, which involves intermittent loosening and inflating of the tourniquet.[8] Previous research reported that this practice significantly reduces the likelihood of capillary flow arrest or the "no-reflow phenomenon". In addition, some studies have also shown that the use of tourniquets in this way increases the ability of muscles to withstand ischaemia for some time, while not reducing ischaemia reperfusion, thereby allowing tourniquets to be used for longer periods.[9]

Immunosuppressive agents, antioxidant agents, steroids, vitamin E, vitamin C and glutamine have been used to prevent IRI related to tourniquet use.[10-12] Various studies have demonstrated the protective effects of these agents against IRI in GA. In one study on tourniquet-induced IRI in anaesthesia, propofol and total intravenous anaesthesia were administered to one group of patients undergoing limb surgery, and inhalation anaesthesia with isoflurane were administered to

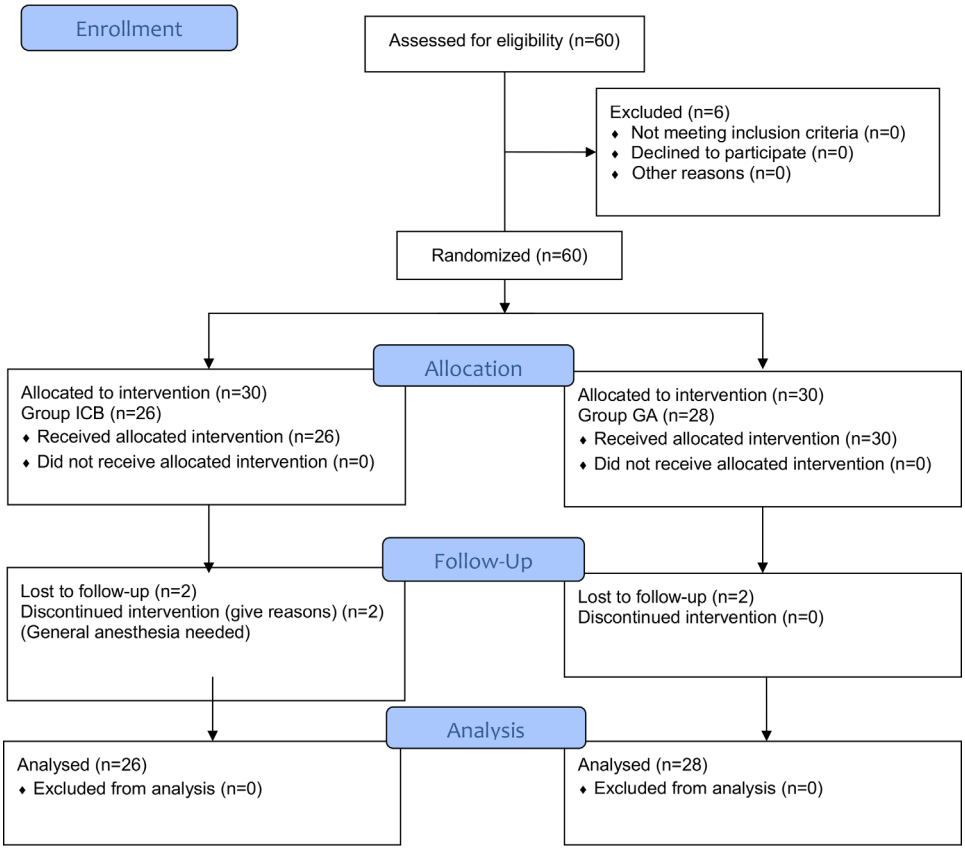

Figure 1. CONSORT flow diagram (group ICB, infraclavicular block, group GA, general anaesthesia).

another group. Malondialdehyde (MDA) levels, which are an important marker of reperfusion injury, were significantly lower in the propofol group.[13] Propofol is chemically similar to vitamin E, an endogenous antioxidant, and butylated hydroxytoluene, a free radical scavenger.[14] Previous research demonstrated that propofol protected erythrocytes against oxidative stress. Propofol accumulates in biomembranes with the rapid occurrence of radical scavenging activity due to the release of a hydrogen atom from the hydroxyl group.[15] Other studies have shown that propofol had high lipid solubility and that it accumulated in lipophilic membranes, which are very sensitive to oxidative damage, and it increased the antioxidant capacity of tissues.[16,17] Runzer et al.[18] demonstrated the antioxidant properties of propofol in different organs. Another study showed that the antioxidant effect of propofol was significantly greater than that of sevoflurane and that propofol reduced IRI caused by free oxygen radicals.[19] Studies have also shown that propofol reduced the pro-inflammatory response in sepsis.[20]

Another study showing the effects of volatile agents on IRI showed that inhalation anaesthetics protected IRI in cardiomyocyte cells by selectively activating ATP-sensitive potassium (K^{ATP}) channels via

Table 1. Characteristics of the patients

	Group ICB (n=26)	Group GA (n=28)	p-value
Age (year)	38.5±15.7	36.0±13.3	0.537
Gender (M/F)	16/10	17/11	0.788
BMI (kg/m²)	26.0±3.4	26.4±4.0	0.691
ASA status (I//II)	18/8	20/8	0.845
Surgery duration (min)	72.6±20.9	67.4±16.0	0.310
Aesthetic duration (min)	72.6±21.1	73.3±18.3	0.901
Tourniquet time (min)	52.7±13.3	51.0±14.1	0.652

Differences between groups are insignificant (p>0.05). Patients' characteristic and surgical data are given as mean ± standard deviation or number of patients. Group ICB: Infraclavicular block group, Group GA: General anaesthesia group. ASA: American Society of Anesthesiologists, BMI: Body mass index.

Table 2. Comparison of serum TAS, TOS and IMA levels between and within the groups according to T1 and T2 times

	Group ICB (n=26)	Group GA (n=28)	p-value
TAS (mmol Trolox Eq/L)			
T1	1.01±0.29	1.00±0.19	0.862
T2	0.92±0.17	0.92±0.20	0.911
TOS (mmol Trolox Eq/L)			
T1	7.22±4.99	10.16±5.15	0.051
T2	9.00±7.55	10.07±5.09	0.540
IMA (ABSUs)			
T1	0.89±0.37	0.90±0.31	0.954
T2	0.97±0.25	0.94±0.23	0.675

Plasma levels of total antioxidant status (TAS) (μmol H_2O_2 equivalent/L), total oxidant status (TOS) (μmol H_2O_2 equivalent/L) and ischemia-modified albumin (IMA) (absorbance units=ABSUs). From all patients, preoperatively (T1), 15 min before tourniquet inflation and 2 hours (T2) after tourniquet release. Group ICB: Infraclavicular block group, Group GA: General anaesthesia group. No statistically significant difference between or within the groups (p>0.05).

Table 3. Comparison of serum TAS, TOS and IMA levels between and within the groups according to the tourniquet times (0-60 and 61-120 minutes)

	Group ICB, (n=26)			Group GA, (n=28)		
	0-60 min, (n=11)	61-120 min, (n=15)	p-value	0-60 min, (n=13)	61-120 min, (n=15)	p-value
TAS (mmol Trolox Eq/L)						
T1	0.95±0.14	1.04±0.44	0.744	1.03±0.13	0.97±0.23	0.505
T2	0.91±0.18	0.95±0.14	0.617	0.95±0.20	0.88±0.20	0.539
TOS (mmol Trolox Eq/L)						
T1	7.93±4.97	5.29±4.86	0.239	9.55±4.26	10.86±6.12	0.431
T2	9.45±8.15	7.76±6.01	0.621	10.03±3.99	10.12±6.31	0.388
IMA (ABSU)						
T1	0.85±0.40	0.99±0.27	0.409	0.93±0.36	0.85±0.23	0.511
T2	0.92±0.21	1.10±0.31	0.109	0.97±0.28	0.91±0.18	0.963

Plasma levels of total antioxidant status (TAS) (μmol H_2O_2 equivalent/L), total oxidant status (TOS) (μmol H_2O_2 equivalent/L) and ischemia-modified albumin (IMA) (ABSUs), according to the tourniquet times (0-60 and 60-120 minutes). Group ICB: Infraclavicular block group, Group GA: General anaesthesia group. No statistically significant difference between and within the groups (p>0.05). ABSU: Absorbance units.

protein kinases.[21] Lucchinetti et al.[22] suggested that sevoflurane (0.5-1%) administered at sedative concentrations in healthy volunteers provided protection against endothelial damage by acting on leukocytes and preventing leukocyte activation and leukocyte adhesion. Another study on 20 patients who underwent elective coronary artery bypass surgery showed results which further supported the cardio-protective effects of sevoflurane.[23] In a study on thoracic surgery patients, at the 6th postoperative hour, the IMA level in a sevoflurane group was lower than that in a propofol group. Thus, the authors concluded that sevoflurane was superior to propofol in preventing IRI.[24] Julier et al.[25] also found that sevoflurane preserves myocardial and renal functions. Budić et al.[26] measured levels of MDA, a lipid peroxidation product, and the activity of an antioxidant enzyme, catalase, which is one of the first defence mechanisms against free radicals. They concluded that continuous propofol infusion and regional anaesthesia techniques attenuate tourniquet-induced IRI in paediatric extremity surgery.

Several studies have shown that remifentanil significantly reduced apoptosis in hepatic cells, protected mitochondrial cells against oedema and protected membranes against IRI, with the authors concluding that remifentanil had protective properties against IRI in liver and intestinal cells.[27,28]

Brachial plexus blockade increases blood flow in the extremity and in replanted digits by preventing neurally mediated spasm, and it is often used to provide sympathectomy and to improve blood flow when vascular insufficiency occurs.[29]

A previous study investigated ischaemia injury in patients undergoing elective knee surgery who received sevoflurane and GA or spinal anaesthesia. Similar tourniquet times were used in both groups. The authors reported that using GA with sevoflurane and nitrous oxide was associated with less oxidative stress than using spinal anaesthesia in their in vivo ischaemia-reperfusion model. In another study which compared sevoflurane and spinal anaesthesia, sevoflurane caused less oxidative stress than spinal anaesthesia.[19,20]

Some studies have also shown that lidocaine provided protection against oxidative stress in erythrocytes. However, only high doses of bupivacaine and ropivacaine provided protection against the harmful effects of oxidative stress.[30] In our study, we showed that there is no significant difference for tourniquet-induced IRI between the ICB group with the use of a mixture prilocaine and bupivacaine and the GA group.

In contrast to local anaesthesia and GA, brachial plexus blockade increases blood flow in the extremity and in replanted digits by preventing neurally mediated spasm. Brachial plexus blockade is often used to provide analgesia and sympathectomy and to improve blood flow when vascular insufficiency occurs. Brachial plexus blockade increases blood flow in the extremity and in replanted digits by preventing neurally mediated spasm.[31,32]

There are only a few studies on the levels of IMA, an indicator of IRI, in extremity surgery. In one study, MA and myoglobin levels in serum samples before knee arthroscopy using a tourniquet were significantly higher than those after surgery.[14] Another study suggested that the administration of both ketamine and lidocaine infusions may significantly decrease skeletal muscle IRI-related high lactate and IMA levels.[33] In our study, we found no significant difference in IMA levels in the pre-operative and post-operative samples.

In our ICB group, we used no systemic aesthetic drugs, and afterwards, similar TAS, TOS and IMA levels were observed in this group. In addition, in our GA group, which effectively represented the control group, we used sevoflurane as an inhaler agent during induction.

Study Limitations

In terms of strengths, standardization was achieved by selecting patients who had no history of trauma and no systemic inflammatory disorders or planned elective procedures. The limitations included the small number of patients, the single centre nature of this study and the measurements of post-operative TAS, TOS and IMA levels only once (i.e. 120 min) after surgery. We think that more significant results may be obtained in studies involving larger numbers of patient, and measuring TAS, TOS and IMA levels over longer post-operative time periods.

CONCLUSION

In this prospective randomized controlled study, ICB and GA were not superior to each other in preventing IRI associated with a tourniquet duration of up to 120 min. However, we believe that more clinical studies with a longer tourniquet times and a larger number of patients are needed in order to clarify these findings.

MAIN POINTS

- Following the opening of the tourniquet at the end of the operation, the re-entry of blood tissue into the general circulation causes a large release of oxygen radicals.
- However, tourniquet-induced ischemic-reperfusion injury (IRI) and its effects on human skeletal muscle cells have been poorly documented.
- Intraclavicular nerve block and general anaesthesia were not superior to each other in preventing IRI associated with a tourniquet duration of up to 120 min.

Ethics Committee Approval: This study was approved by the Ethics Committee of Selçuk University Faculty of Medicine (approval number: 07.03.2018/2018/05).

Informed Consent: All the patients provided informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.T., F.Ç., Design: Ö.T., F.Ç., Supervision: F.Ç., M.S., Materials: F.Ç., H.V., E.P.H., Data Collection and/or Processing: Ö.T., H.V., E.P.H., M.S., Analysis and/or Interpretation: H.V., E.P.H., M.S., Literature Search: Ö.T., F.Ç., İ.K., Writing: Ö.T., İ.K., Critical Review: H.V., İ.K.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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