 Acta Chir Orthop Traumatol Cech. 90, 2023, No. 5, p. 314–322
DOI: 10.55095/ACHOT2023/037

ORIGINAL PAPER
PÙVODNÍ PRÁCE

Effect of Remote Ischemic Preconditioning in Total Knee Arthroplasty on Thiol-Disulfide Balance: a Randomized Controlled Study

Efekt vzdálených ischemických podnětů na thiol-disulfidovou rovnováhu u TP kolena: randomizovaná kontrolovaná studie

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ABSTRACT

PURPOSE OF THE STUDY

The purpose of this study was to minimize tourniquet-induced ischemia-reperfusion injury (IRI) in total knee arthroplasty (TKA) surgery using the remote ischemic preconditioning (RIPC) model, as well as to assess antioxidant balance with thiol-disulfide homeostasis (TDH). The secondary goal is to evaluate the impact of RIPC on TKA clinical outcomes.

MATERIAL AND METHODS

Patients in the ASA I–III group who underwent elective TKA were enrolled in this prospective, randomized, double-blind clinical research. TDH parameters were measured individually in groups with (Group I) and without (Group K) RIPC at the following times: preoperative (T0), right before the pneumatic tourniquet was opened (T1), 1 (T2), 6 (T3), and 24 (T4) hours after it was opened. In addition, at 3-hour intervals, the postoperative pain level was assessed using a visual analog scale (VAS).

RESULTS

This study included 60 cases (Group K; n=30, Group I; n=30). Both groups had equal native thiol, total thiol, disulfide levels, disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios ($p>0.05$ for each). The change in native thiol, total thiol, and disulfide values at T0 and T4 periods, however, was not statistically significant for Group K ($p=0.049$, $p=0.047$, $p=0.037$, and $p=0.217$, $p=0.191$, $p=0.220$, respectively). At the 15th hour, VAS values in group I were considerably lower than in Group K ($p=0.002$).

DISCUSSION

This prospective, randomized, controlled trial examined how RIPC affected tourniquet-induced IRI-induced oxidative stress in TKA surgery. Lower native, total, and disulfide levels at each postoperative time point were significant. RIPC may reduce tourniquet-induced IRI-induced oxidative stress and TDH in TKA surgery. RIPC also reduced postoperative discomfort.

CONCLUSIONS

Our findings suggest that RIPC may protect against the oxidative stress caused by IRI during limb surgery with a tourniquet and improve postoperative clinical outcomes.

Key words: remote ischemic preconditioning, ischemia-reperfusion injury, thiol-disulfide balance, oxidative stress, total knee arthroplasty.

INTRODUCTION

Total knee arthroplasty (TKA) is a surgical procedure used to improve patients‘ mobility and quality of life with advanced knee osteoarthritis. Many key surgical steps and methods are required for successful surgery. By offering a complete view of the bloodless surgical site and the surgical area, pneumatic tourniquet application is often utilized to reduce surgical mistakes, increase cement intertwining, and reduce intraoperative blood loss and surgery time (2, 3). However, tourniquet use can alter normal physiology, leading to various problems (15). An environmentally inflated sleeve, for example, can compress the structures beneath it, resulting in localized mechanical and ischemia damage to the muscles and nerves. Furthermore, tourniquet administration after long ischemia may cause ischemia-reperfusion injury (IRI) due to the activation of proinflamma-

tory cytokines and reactive oxygen species (ROS) during reperfusion (11). IRI is linked to the generation of ROS, which damage cellular components and trigger the lipid peroxidation process (29). Tissue damage caused by ROS generation can activate various defensive mechanisms, potentially leading to serious postoperative problems. As a result, clinicians must make every effort to reduce these consequences.

Ischemia preconditioning is a natural process that protects tissues and organs from ischemic damage by activating several signaling pathways and boosting anti-inflammatory effects (21). Remote ischemia preconditioning (RIPC) is an adaptive response that protects organs against damage caused by various stressors. This response generates brief and transient ischemia events in a distant region before injuring the target organ (12). Clinical research suggests that RIPC can prevent organ damage and improve outcomes in high-risk individuals during surgical operations (13). However, even though the effect of RIPC has been studied in various therapeutic contexts, the underlying mechanism remains unknown.

Thiols are chemical substances that can react with free radicals to protect tissue and cells from free oxygen radical damage (FORs) (6). This operates by allowing oxidant molecules in the media to oxidize thiol groups. The resultant disulfide linkages can be reduced back to thiol groups, preserving the thiol-disulfide equilibrium (9). The dynamic thiol-disulfide balance is important in antioxidant defense, apoptosis, detoxification, enzyme activity modulation, and transcription mechanisms. Thiol-disulfide levels in plasma are a valuable and consistent measure of oxidative stress and antioxidant defense mechanisms (6). Diabetes, cardiovascular illness, cancer, rheumatoid arthritis, chronic renal disorders, Alzheimer‘s disease, multiple sclerosis, and liver diseases have all been studied for the dynamic thiol-disulfide balance (9). These investigations have demonstrated that RIPC protects against organ damage caused by lower extremity ischemia-reperfusion. However, its effect on thiol-disulfide hemostasis is still unknown (22). This prospective, randomized, and controlled clinical study aimed to determine the efficacy of upper extremity RIPC in avoiding tourniquet-induced IRI in TKA patients with dynamic thiol-disulfide homeostasis. We also wanted to see how RIPC affected clinical outcomes like pain score and postoperative analgesic use.

MATERIAL AND METHODS

Enrollment and eligibility

The Republic of Turkey Health Sciences University Hamidiye Clinical Research Board (numbered 21/2 and dated 04.03.2021) and the Konya City Hospital Medical Specialization Training Board approved for this prospective, randomized, controlled, and double-blind efficacy study (numbered 05-13 and dated 06.05.2021). This study, which has the registration number NCT05082207 in the Clinical Trial database, took place between October 2021 and April 2022 after obtaining written informed consent from all patients participating in the study in the Anesthesiology and Reanimation Clinic of Konya City Hospital of the University of Health Sciences and the Orthopedics and Traumatology Clinic.

Inclusion criteria

Patients in the ASA I-III category, aged 18 to 90, will receive TKA under spinal anesthesia at Health Sciences University Konya City Hospital.

Exclusion criteria

Patients with emergency surgery, neurological problems, peripheral vascular disease, concomitant surgery, malignancy, and active infection status were excluded from the study.

Research protocol

Group I is the RIPC group.
Group K is the control group.

RIPC implementation

In Group I, a conventional blood pressure sleeve (F. Bosch Konstante II) was wrapped around the upper arm. Systolic blood pressure plus 50 mmHg (for 30 minutes) was administered three times with a 5-minute inflating and deflation cycle (28). The blood pressure sleeve was put over the upper arm but left deflated at 0 mmHg in Group K (for 30 minutes). The cuffed sleeve was applied to the patient‘s arm following the non-invasive blood pressure measurement recommendations (25).

Anesthesia management

All patients underwent the same conventional perioperative anesthesia-analgesia-surgical protocols. The patient files contained demographic and surgical data (surgery time, tourniquet time, bleeding and transfusion, postoperative analgesic use, pain scores, and so on). To ensure blinding, the researchers who performed the RIPC and collected the patients‘ demographic and surgical data were always different.

We did not use any premedication before the surgery. After venous cannulation, monitoring was used in the operating room with a 20 G venous cannula, ECG, oxygen saturation (SpO2), non-invasive blood pressure, and end-tidal carbon dioxide ($EtCO_2$). A 25 G spinal needle was used to give spinal anesthetic at the L3-4 or L4-5 vertebrae in the sitting posture (12 mg 0.5% hyperbaric bupivacaine (20 mg/4 ml ampoule containing 0.5% Spinal Heavy Injection Solution of Bustesin, Vem laç) + 75 mcg morphine). The patient was immediately placed in the supine posture following the application. The pinprick test was used to assess sensory block by losing sensitivity to cold at appropriate dermatomal levels. The modified Bromage scale was used to assess the motor block. The proce-

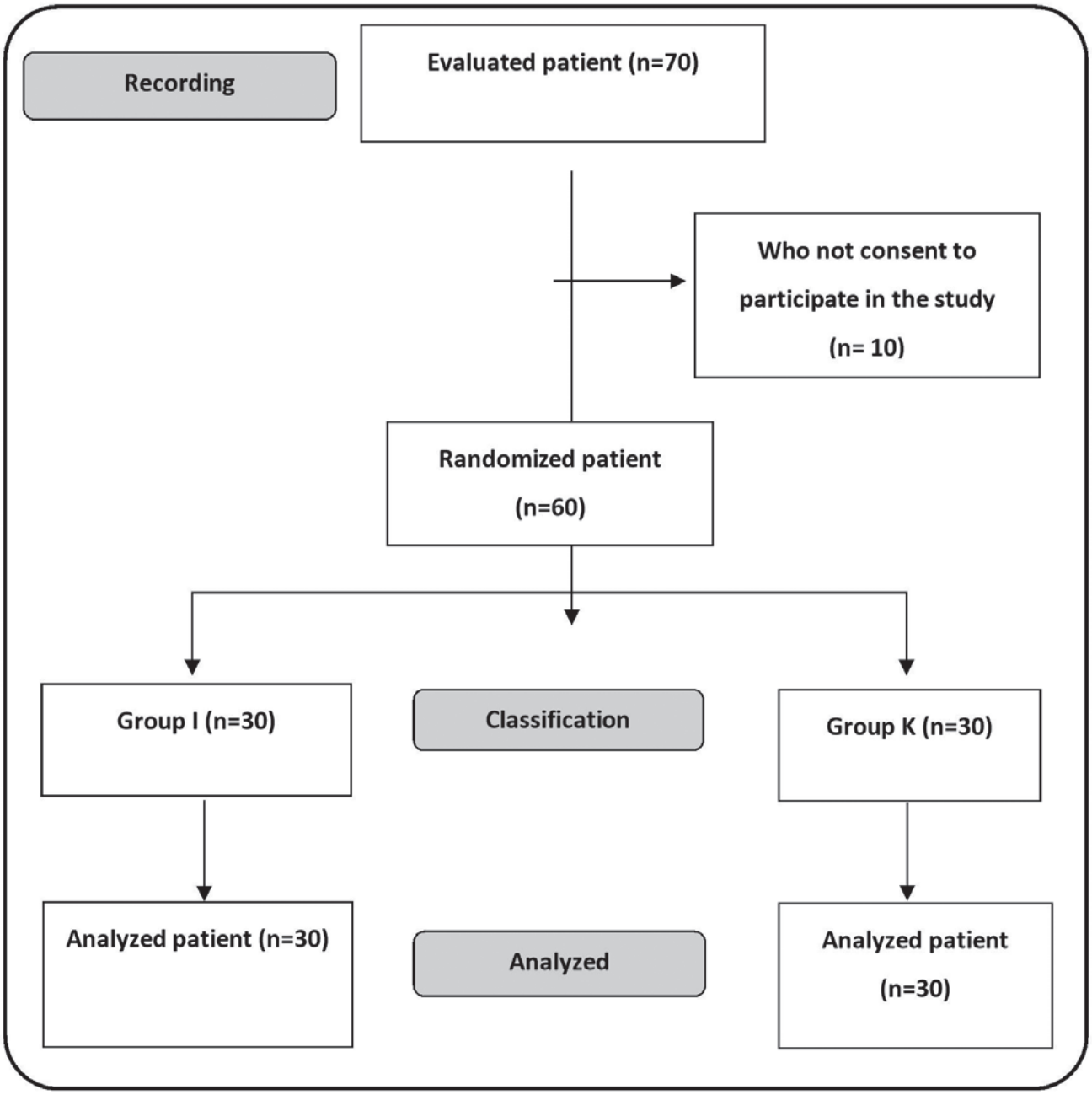

Fig. 1. Consort diagram.

dure began when the sensory block in the T4 dermatome was reached.

Hypotension was defined as a 20% or more reduction in mean blood pressure from baseline or a mean blood pressure less than 60 mmHg. When hypotension set in, 10 mg of ephedrine was injected intravenously (IV). A heart rate of 40 beats per minute or below was considered bradycardia (5). When bradycardia occurred, 0.5 mg of atropine was administered intravenously. At 5-minute intervals, the patient‘s mean arterial blood pressure (MABP), systolic arterial blood pressure (SABB), diastolic arterial blood pressure (DABP), SpO2, and heart rate were recorded.

The patient was positioned supine, and the extremity to be operated on was elevated before the pneumatic tourniquet (Promedic DTS-3000) was placed at the intersection of the proximal third of the femur and the midline of the femur. An Esmark bandage was used to achieve 100 mmHg over the systolic arterial blood pressure following blood discharge (30). The tourniquet‘s inflation and deflation times were recorded.

Surgical procedure

TKA was performed utilizing a medial parapatellar approach and a cemented implant that protects the posterior cruciate ligament.

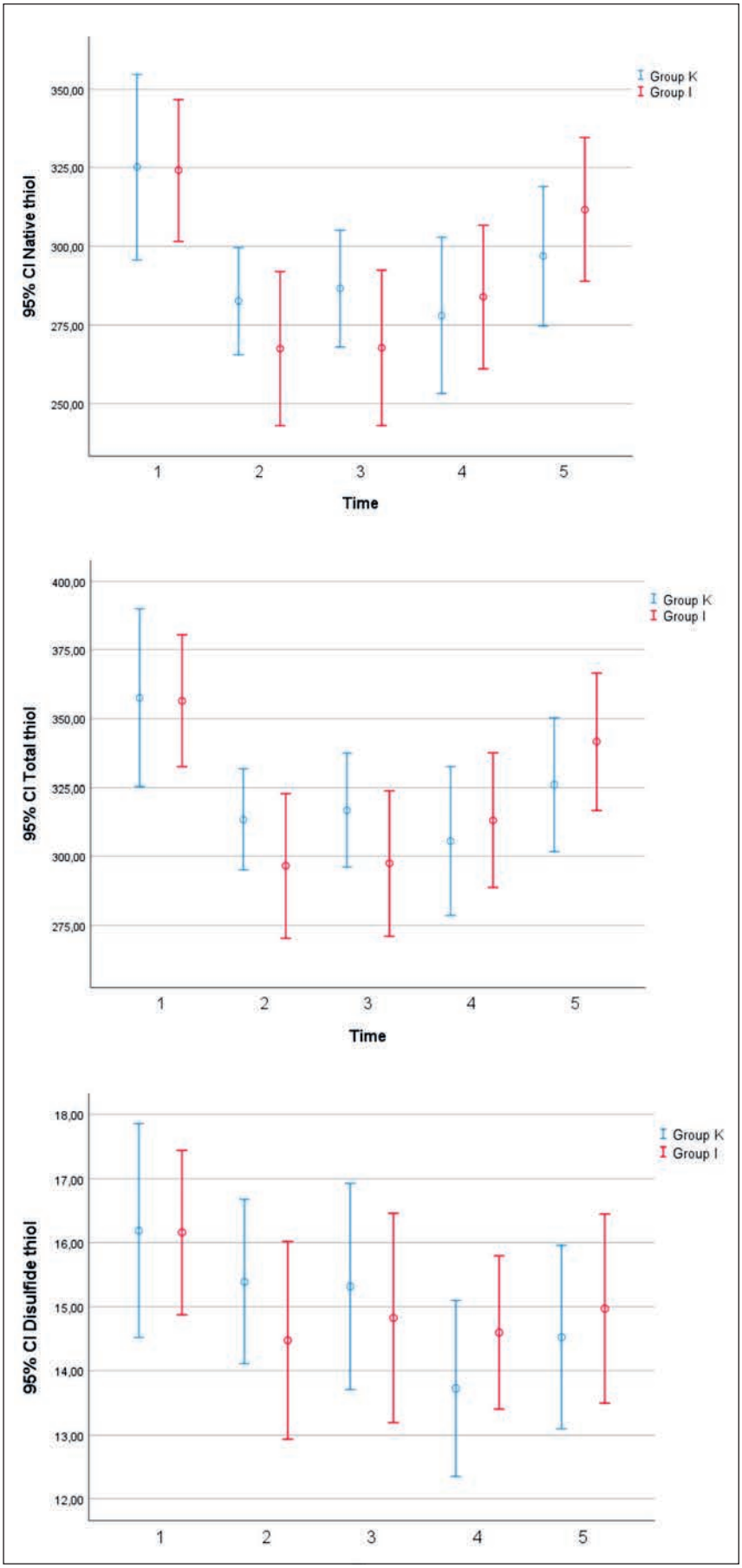

Fig. 2. Native thiol, total thiol and disulfide thiol values in groups according to time.

Thiol-disulfide study

T0 (preoperative baseline value), T1 (immediately before tourniquet opening), T2 (postoperative 1 hour), T3 (postoperative 6 hours), and T4 (postoperative 24 hours) (postoperative 24 hours). 2 ccs of blood were drawn from each patient and centrifuged for 10 minutes at 1500 rpm. Serum and plasma samples were separated, and serum samples were collected and kept at -80°C until biochemical analysis. The level of thiol-disulfide homeostasis was determined using the automated spectrophotometric method developed by Erel and Neşeliolu after collecting all sera (7).

The sodium borohydride technique reduced the disulfide bonds produced during oxidation to free functional thiol groups. By interacting with formaldehyde, excess sodium borohydride was deactivated. At 412 nm, the amount of native thiol and the total amount of thiol produced by reducing disulfide bonds was quantified using DTNB (5,5‘-dithiol bis (2-nitrobenzoic acid)) chromogen. The amount of dynamic disulfide was half the difference between total and native thiol. The calculating approach yielded disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios.

Protocol for standard analgesia and rescue analgesia

Following spinal anesthesia, the usual analgesic regimen for TKA involves 20 mg tenoxicam, 1 g paracetamol, and 20-30 cc local anesthetic (0.25% bupivacaine) with a 22 G block needle 80-100 mm long in the supine position, with ultrasonography and neurostimulator at the end of the surgical procedure. VAS, nausea-vomiting score, the requirement for rescue analgesia, and antiemetic needs were documented in postoperative follow-ups (0, 3, 6, 9, 12, 15, 18, 21, and 24 hours). In the postoperative recovery unit, patients with VAS scores of 4 or above were given 1 mg/kg IV tramadol as rescue analgesia. In addition, both groups received par-

acetamol 1 g 3x1 IV and tenoxicam 20 mg 1x1 IV as part of a normal analgesic protocol within the first 24 hours of admission. During the pain level follow-up in the ward, IV 1 mg/kg tramadol was delivered as rescue analgesia to patients with VAS ratings of 4 or above.

Assessment of postoperative pain

A visual analog scale (VAS) was used to assess the patient‘s level of pain. The VAS is a pain rating system in which patients report the number (0–10) that best describes the intensity of their discomfort. Zero symbolizes „no pain at all,“ while ten signifies „worst anguish“.

Analyses of nausea and vomiting

Patients rated their nausea on a four-point scale: 0 for no nausea, 1 for mild nausea, 2 for moderate nausea, and 3 for severe nausea. In situations where the nausea score was 2, IV 4 mg ondansetron was given.

Measurement of sample size

Based on past research for sample size analysis, a difference in postoperative total thiol levels of at least 15% between groups would be clinically meaningful (4,27). The sample size for the t-test model in independent groups was determined as 58 patients for 95% power and a maximum 5% type 1 error in the calculation conducted using Cohen‘s D effect size of 0.975, based on the mean postoperative total thiol level of 264.640.7. Taking the dropout rate into account, 60 patients (30 in each group) were enrolled in the study.

Statistical analysis

IBM Social Sciences Statistical Package (IBM-SPSS Inc., Chicago, IL, USA) The data was analyzed with the 22.0 program. The Kolmogorov-Smirnov test determined whether the data was suitable for normal distribution. According to their distribution state, continuous variables are given as the mean and standard deviation (or median (25-75 percentile) in -non-normally dis-

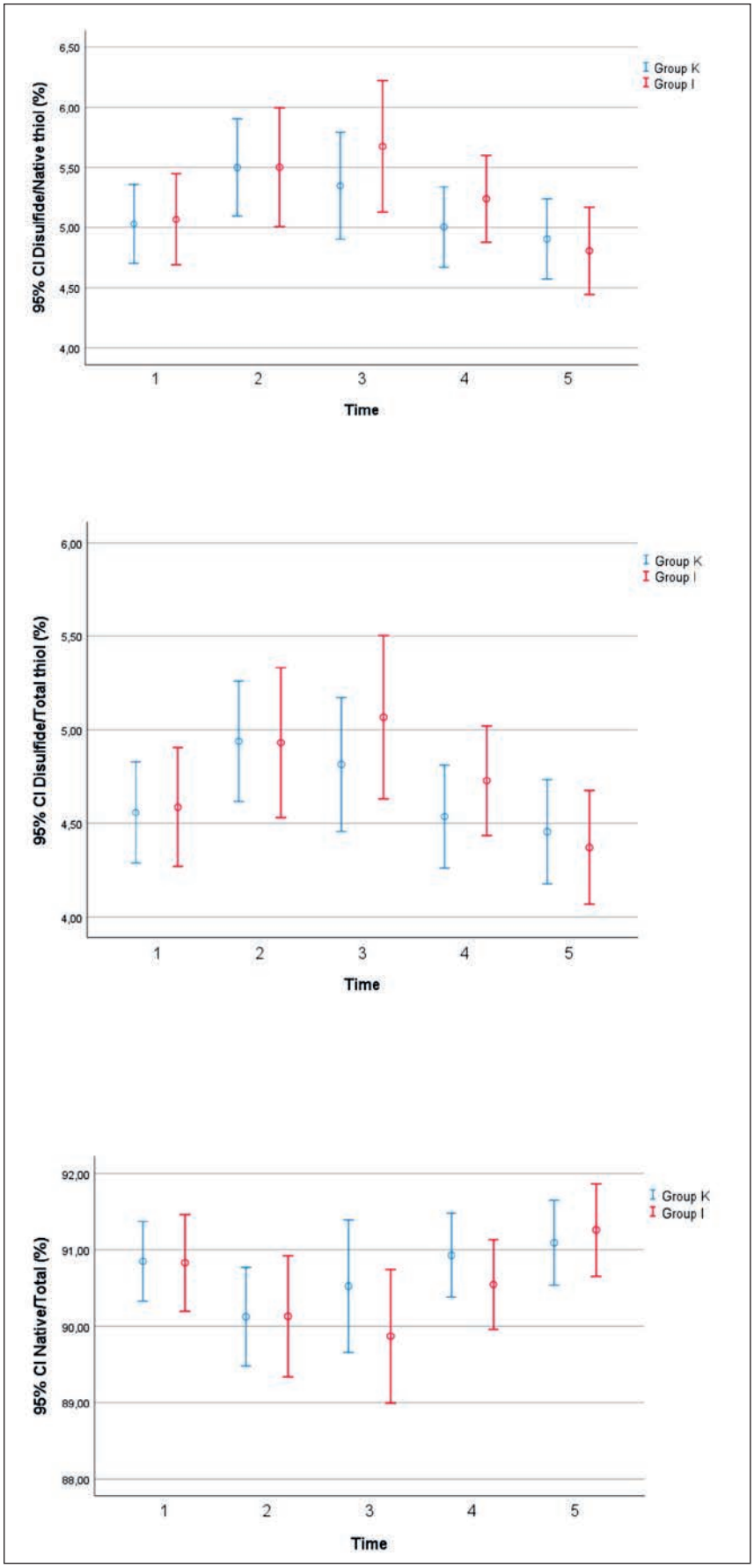

Fig. 3. Disulfide/native thiol, disulfide/total thiol and native/total thiol values in groups according to time.

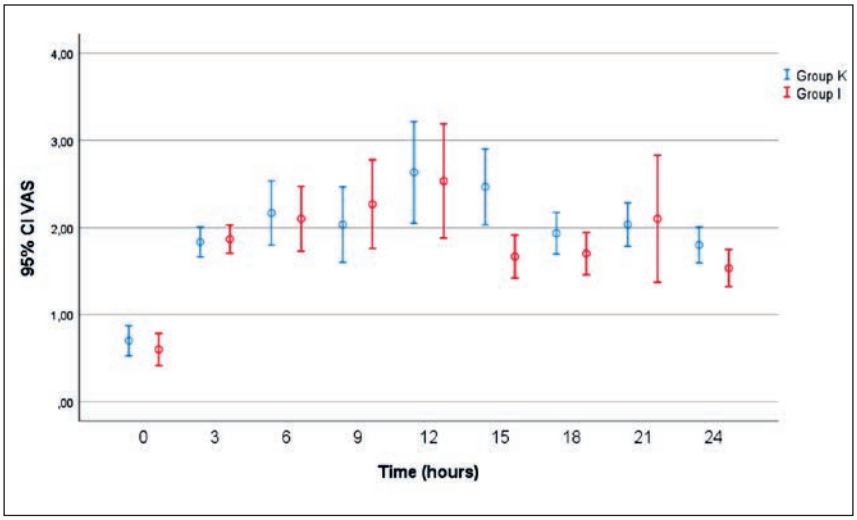

Fig. 4. VAS (Visual Analog Scale) values in groups according to time.

tributed). Categorical variables, on the other hand, are stated as numbers and percentages. In the study of continuous variables, a t-test was used in independent groups if parametric test assumptions were acceptable; otherwise, a Mann-Whitney U-test was used. The Pearson Chi-square and Fisher's exact tests were used to comparing categorical variables. ANOVA was employed for repeated measurements taken at different times by the groups. The data were analyzed at the 95% confidence range, and the statistical significance was set at $p<0.05$.

RESULTS

Seventy cases met the inclusion criteria for this study. Ten of the cases refused to participate in the study. As shown in Figure 4, the remaining 60 patients were analyzed in the study (Group K; n=30, Group I; n=30). In terms of ASA risk class, presence of comorbidities, tourniquet time, surgical procedure time, and intraoperative findings, Group K and Group I demographic data were statistically equivalent ($p>0.05$ each) (Table 1). For 1 hour, intraoperative hemodynamic data (heart rate, blood pressure, end-tidal carbon dioxide ($EtCO_2$) (%), SpO2) were recorded every 5 minutes. This data was statistically similar in Group K and

Table 1. Demographic characteristics, duration of tourniquet application, surgical procedure, and intraoperative results

Characteristics		Group K (n=30)	Group I (n=30)	p
Age		63.8±6.3	60.7±8.3	0.118
Gender	Man	7 (23.3%)	2 (6.7%)	0.145
	Woman	23 (76.7%)	28 (93.3%)	
Height (cm)		163.1±7.3	162.1±6.9	0.599
Weight (kg)		75.1±8.0	75.2±7.3	0.960
BMI ($kgcm^{-2}$)		28.3±2.5	28.6±2.3	0.556
ASA	1	5 (16.7%)	13 (43.3%)	0.062
	2	20 (66.7%)	15 (50%)	
	3	5 (16.7%)	2 (6.7%)	
Surgical side	Right	14 (46.7%)	12 (40%)	0.602
	Left	16 (53.3%)	18 (60%)	
Additional disease	No	6 (20%)	13 (43.3%)	0.052
	Yes	24 (80%)	17 (56.7%)	
Bronchial asthma	No	28 (93.3%)	24 (80%)	0.254
	Yes	2 (6.7%)	6 (20%)	
Diabetes mellitus	No	21 (70%)	27 (90%)	0.053
	Yes	9 (30%)	3 (10%)	
Hypertension	No	13 (43.3%)	19 (63.3%)	0.121
	Yes	17 (56.7%)	11 (36.7%)	
Surgical time (minute)		58.3±6.9	58.0±6.5	0.848
Tourniquet time (minute)		63.3±6.9	63.0±6.5	0.848
Amount of intraoperative bleeding (ml)		100 (50-150)	100 (50-150)	0.641
Fluid is given intraoperatively (ml)		1000 (1000-1100)	1000 (1000-1000)	0.450

* Data are presented as mean±standard deviation or n (%).*(kg: kilogram, BMI: body mass index, ml: milliliter, mg: milligram, ASA: American Society of Anesthesiologists)*

Table 2. Ondansetron usage, nausea, and vomiting in the groups

Characteristics		Group K (n=30)	Group I (n=30)	p
Ondansetron (mg)		4 (0-4)	4 (4-8)	0.198
Use of antiemetic agents	No	9 (30%)	6 (20%)	0.371
	Yes	21 (70%)	24 (80%)	
Vomiting	No	18 (60%)	18 (60%)	1
	Yes	12 (40%)	12 (40%)	
Nausea	No	10 (33.3%)	6 (20%)	0.243
	Yes	20 (66.7%)	24 (80%)	

* Data are presented as n (%) or median (25–75 percentile). (mg: milligram)

Group I throughout the trial (p>0.05 for each). Furthermore, for each parameter, the change over time (time x group interaction) in the groups was similar (p>0.05 for each).

In Group K and Group I, there was no statistically significant difference in the following parameters: Native thiol, Total thiol, Disulfide, Disulfide/Native thiol, Disulfide/Total thiol, and Native thiol/Total thiol (p>0.05). There was no statistically significant difference in changes for all parameters in either group over time. While the group effect and time-group interaction were statistically significant (p0.05), there was no statistically significant difference in the group effect and time-group interaction (p>0.05) (Fig. 2, 3).

Native thiol, Total thiol, and Disulfide values were lower at T0 than at T4 for both Group K and Group I. Although this drop was greater and statistically significant (p0.05) in Group K, it was not significant in Group I (p>0.05). Furthermore, there was no statistically significant difference in the time-group interaction for any of the characteristics (p>0.05; Fig. 2). Furthermore, for both Group K and Group I, there was a decrease in the Disulfide/Native thiol, Disulfide/Total thiol, and Native thiol/Total thiol values at T4 compared to time T0. Although the drop in Group K was smaller, it was not statistically significant (p>0.05) in either Group K or Group I. For both Group K and Group I, the Native thiol/Total thiol parameter showed an increase in values evaluated at T4 time compared to T0 time. Although group I increased more than Group K, the difference was not statistically significant (p>0.05). Furthermore, there was no statistically significant difference in all parameters in the time-group interaction (p>0.05; Fig. 3).

The VAS values in group I was considerably lower than those in Group K at the 15th postoperative hour (p=0.02), whereas the VAS values in the two groups were similar at other times (p>0.05). Neither group had a statistically significant difference in VAS values over time (p>0.05). While the time effect in the groups was statistically significant (p=0.003), the time-group interaction was not (p=0.154 and p=0.289, respectively; Fig. 4). The frequency of patients requiring rescue analgesia within the first postoperative 24 hours was comparable in Group K (33.3%) and Group I (30%) (p=0.781).

Postoperative nausea and vomiting incidence rates and antiemetic needs were comparable in both groups (p>0.05; Table 2).

DISCUSSION

The effects of RIPC on oxidative stress caused by tourniquet-induced IRI in TKA surgery were studied in this prospective, randomized, controlled trial. A significant study finding was lower native thiol, total thiol, and disulfide levels at each postoperative time point. When compared to preoperative measured values, this impact was consistent in both the control and RIPC intervention groups. Furthermore, in the Group without RIPC, the change in baseline, as well as 24-hour serum native thiol, total thiol, and disulfide values, were statistically significant. As a result, RIPC may protect against oxidative stress and TDH caused by tourniquet-induced IRI in TKA surgery. Another advantage of the RIPC intervention was that it was related to lower postoperative pain assessments.

TKA is an effective surgical treatment for knee osteoarthritis that relieves pain and improves the quality of life. However, the use of tourniquets during surgery is still debatable (1). Intraoperative tourniquet application has several advantages, including reduced intraoperative blood loss and a reduced requirement for postoperative blood transfusion. However, it has some drawbacks, including early postoperative pain, delayed recovery (2), skeletal muscle injuries, and IRI in distant important organs. Using a tourniquet during orthopedic surgery has been shown to reduce oxidative damage. Mas et al. compared spinal anesthesia to general anesthesia and found that general anesthesia increased oxidative stress (18). Several research has been conducted to minimize oxidative stress utilizing various antioxidant compounds. There is currently no evidence that mannitol decreases ROS. On the other hand, N-acetylcysteine has been linked to decreased lipid peroxidation and, as a result, oxidative stress (14). Malondialdehyde levels, a hallmark of oxidative stress, were lower in patients who underwent bilateral TKA surgery and re-

ceived high doses of vitamin C, according to a study by Lee et al. Furthermore, the arterial oxygen pressure was higher in this investigation (16).

Ischemic preconditioning (IPC) is one of the treatments utilized to minimize oxidative stress produced by tourniquet use in patients undergoing knee surgery. Murphy et al. discovered a protective genetic response in muscle samples from 10 of 20 TKA patients who received IPC (20). Lin et al. found that lower extremities surgery and IPC reduced lipid peroxidation, systemic inflammatory response, and pulmonary dysfunction (17).

Although the mechanism of RIPC is unknown, certain experimental and clinical investigations demonstrate that RIPC-induced local tissue injury can activate humoral mediators (adenosine, bradykinin, antioxidants) and initiate neuronal signal transmission with cytoprotective effects (8).

It may also protect endothelial cells via systemic anti-inflammatory and antithrombotic actions. The number of ischemia cycles and the duration of each ischemic period determines the efficiency of IPC. Three ischemia cycles in 5-minute ischemic periods produced the best results (24). As a result of this observation, our study‘s RIPC model consisted of three cycles of five minutes of reperfusion after five minutes of ischemia. Compared to baseline data, the considerable reduction in serum thiol, total thiol, and disulfide at the 24th hour in the control group support the hypothesis that the dynamic redox system is considerably influenced. These side effects could be attributed to the type of anesthetic utilized, surgical stress, and IRI related to the tourniquet in TKA. Furthermore, RIPC facilitates this procedure.

Thiol-containing chemicals are essential for preventing oxidative stress. Thiols are rapid electron receptors with negative standard reduction potentials. When an oxidant reacts with a thiol group, the oxidant is converted into an oxidized thiol by-product, a less dangerous disulfide. During oxidation processes, thiol levels fall linearly. As a result, dynamic TDH measurements can be used to illustrate the oxidative status of plasma clinically (7). While TDH can only measure one side of the reaction, a novel calorimetric approach devised by Erel and Neselioglu in 1979 allowed both variables to be evaluated independently and collectively, allowing for evaluation of both individually and collectively (7). This study found that levels of native thiol, total thiol, and disulfide did not rebound to preoperative levels 24 hours following surgery. When having surgery, lower native and total thiol levels indicate that these molecules are consumed due to oxidative stress. Monitoring thiol/disulfide homeostasis during surgery could be useful as an early screening test to determine appropriate treatment options. It can also be used to identify individuals afflicted by oxidative stress and measure the level of oxidative stress. The local inflammatory response to IRI caused by edema and tourniquet use in the extremity following TKA surgery may have a role in developing postoperative discomfort. Previous research has shown that RIPC may enhance postoperative pain control in individuals undergoing knee arthroplasty. The median reported pain scores of the extremity to be treated were statistically significantly lower than the control group in a study by Memtsoudis et al. on 34 patients who underwent TKA surgery under combined spinal epidural anesthesia and postoperative femoral block, and there was no difference between epidural and oral analgesic consumption (19). In another study, Orban et al. discovered that individuals undergoing IPC had reduced opioid intake than those undergoing ligamentoplasty (23). In line with earlier research, we discovered that pain levels during the 15th postoperative hour were significantly lower in the RIPC group. Although the mechanism by which pain is reduced is unknown, RIPC probably lowers inflammation and, eventually, tissue damage during the reperfusion period. Schoen et al. demonstrated that measuring IPC levels before applying a long-term tourniquet to a rat‘s limb lowered the degree of apoptotic cell death and inflammation. Microcirculation has also been enhanced. Furthermore, they demonstrated decreased pain sensation and motor performance in rats receiving Grade IPC (26).

A small number of studies documented RIPC-related adverse effects or problems. Paresis, paleness, decreased capillary filling, skin patches, and bullae formation due to ischemia may occur in the extremity due to RIPC. Rhabdomyolysis can also occur as a result of tourniquet-applied muscle compression. Furthermore, the increased potassium, myoglobin, and lactate in circulation may create metabolic problems. Skin petechiae were somewhat more common in patients who received RIPC than in the control group, according to Housenloy et al. (10). On the other hand, our study found no local problems in individuals undergoing RIPC in the extremities.

The current study is the first to investigate the association between RIPC and TDH in patients following tourniquet TKA surgery. There were various constraints. First and foremost, ours was a single-center study. Second, we did not compare our findings to other oxidative stress measures such as lipid hydroperoxide, total antioxidant status, and oxidative stress index. Third, the extent of late-stage IRI was impossible to assess because of the rapid discharge on postoperative day two or day three. Finally, the results of younger demographic groups are not reflected in this study due to the nature of the surgical treatment. However, the same age distribution of the groups suggests that this limitation will have little effect on the study‘s findings.

CONCLUSIONS

According to the findings of this study, RIPC may have a protective effect against oxidative stress generated by IRI in patients having TKA surgery with a tourniquet. At the same time, this method may improve clinical results by lowering postoperative pain levels. RIPC is a simple, low-cost, non-invasive technology

now accessible for clinical use. However, more research on RIPC and TDH is required before this method may be widely adopted.

Author contributions

MNA: data acquisition, investigation, writing – review & editing. MY: data acquisition, investigation, writing – review & editing. ZS: data acquisition. OS: data acquisition. MST: formal analysis, software, visualization, writing – review & editing. YT: conceptualization, writing – review & editing. BK: data acquisition, investigation, writing – review & editing.

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