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The Effect of Spinal and General Anesthesia on Thiol-Disulfide Balance During Ischemia/Reperfusion of the Leg in Patients Undergoing Knee Replacement Surgery

Diz Replasmanı Ameliyatı Altındaki Hastalarda Bacağın İskemi/Reperfüzyonu Sırasında Tiyol-Disülfit Dengesi Üzerine Spinal ve Genel Anestezinin Etkisi

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ABSTRACT

Objective: Surgical trauma causes serious neuroendocrine and cytokine activity. In addition, the free oxygen radicals formed because of the ischemia/reperfusion injury resulting from applying and releasing the tourniquet (TQ) cause oxidative stress. Thiol and disulfide are among the new oxidative stress parameters used reliably in recent years. The aim of this study was to compare thiol-disulfide balance in general and spinal anesthesia, which are frequently used in total knee replacement (TKR) surgery.

Methods: Fifty six patients aged 60-74 years scheduled to undergo TKR were randomly allocated to the general anesthesia (n=26) and spinal anesthesia (n=30) groups. The tourniquet (TQ) was applied for the TKR procedure after collecting a preanesthetic blood sample (T1). Blood samples were also collected at 5 minutes (T2) and 40 minutes (T3) after TQ release and at postoperative 24 hours (T4) to analyze native thiol, total thiol, disulfide, disulfide/native thiol ratio, disulfide/total thiol ratio, and native thiol/total thiol ratio. All patients had intravenous patient-controlled analgesia during the postoperative period. Mean arterial pressure, TQ times, and Visual Analogue Scale (VAS) scores were recorded. Decrease in thiol and increase in disulfide in the thiol-disulfide balance were recorded as oxidative stress indicators.

Results: There was no difference between the groups in terms of VAS and analgesic consumption at the end of 24 hours. The general anesthesia group had higher native thiol, total thiol, and native thiol/total thiol ratio and lower disulfide, disulfide/native thiol ratio, and disulfide/total thiol ratio at all time points compared to the spinal anesthesia group.

Conclusion: Assessment in terms of thiol-disulfide balance suggests that general anesthesia had a favorable effect on oxidative stress.

Keywords: General anesthesia, oxidative stress, spinal anesthesia, thiol-disulfide, tourniquet time, visual analogue scale

ÖZ

Amaç: Cerrahi travmaya stres cevap olarak gelişen ciddi nöroendokrin ve sitokin aktiviteleri oluşur. Buna ek olarak turnike indirilmesiden sonra gelişen iskemi/reperfüzyon injurisi ile oluşan serbest oksijen radikalleri oksidatif strese neden olur. Tiyol ve disülfit son zamanlarda güvenle kullanılan yeni oksidatif stres parametrelerinden biridir. Bu çalışmanın amacı, total diz protezi (TDP) cerrahisinde sıklıkla kullanılan genel ve spinal anestezideki tiyol-disülfit dengesini karşılaştırmaktır.

Yöntem: Çalışmada etik kurul onayı alındıktan sonra 60-74 yaşları arasında TDP yapılacak 56 hasta randomize olarak genel anestezi (n=26) ve spinal anestezi (n=30) grubuna ayrıldı. Preanestezik olarak (T1) kan örneği alındıktan sonra cerrahi sırasında turnike uygulandı. Turnike indirilmesi sonrası 5. (T2) ve 40. dakikalarda (T3) ve 24. saatte (T4) doğal tiyol, toplam tiyol, disülfit, disülfit/doğal tiyol oranı, disülfit/toplam tiyol oranı ve doğal tiyol/toplam tiyol oranı bakılmak üzere kan örnekleri toplandı. Bütün hastalara postoperatif süreçte intravenöz hasta kontrollü analjezi uygulandı. Ortalama arter basıcı, turnike süreleri, Vizüel analog skala (VAS) skorları kaydedildi. Tiyol-disülfit dengesinde tiyol azalması ve disülfit artması oksidatif stres indikatörü olarak kaydedildi.

Bulgular: Yirmi dört saat sonundaki VAS ve analjezik tüketiminde gruplar arasında fark yoktu. Genel anestezi grubunda ölçülen tüm zamanlarda doğal tiyol, toplam tiyol, doğal tiyol/toplam tiyol düzeyinde artma, disülfit, disülfit/doğal tiyol ve disülfit/toplam tiyol oranında azalma vardı.

Sonuç: Tiyol-disülfit dengesi açısından değerlendirme, genel anestezinin oksidatif stres üzerinde olumlu bir etkisi olduğunu düşündürmektedir.

Anahtar sözcükler: Genel anestezi, oksidatif stres, spinal anestezi, tiyol-disülfit, turnike süresi, vizuel analog skala

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INTRODUCTION

Total knee replacement (TKR) is a surgical treatment applied to improve the quality of life and mobility of patients with advanced knee osteoarthritis. Its prevalence has increased in recent decades and continues to increase (1,2). Muscle atrophy following the use of an intraoperative pneumatic tourniquet (TQ) results in deficits in muscle strength in the early postoperative period and subsequent impairment in post-TKR rehabilitation. A TQ is used to achieve a bloodless surgical field for extremity surgeries. However, applying the TQ changes the normal physiology and is associated with several complications (3). Tourniquet inflation initiates ischemia in the extremity, and its release can induce ischemia-reperfusion injury. The injury affects not only the skeletal muscle locally, but also the systemic circulation and distant vital organs including the brain, heart, lungs, and kidneys. Reperfusion can increase the damage secondary to ischemia. In addition, ischemia increases the production of reactive oxygen species (ROS) and promotes a pro-inflammatory state, which in turn increases the tissues that are susceptible to reperfusion injury. In addition, serious neuroendocrine and cytokine activity occurs in response to surgical trauma, leading to the overproduction of free oxygen radicals compared to normal physiological levels (4,5). Identifying and using anesthesia methods that do not exacerbate oxidative stress may contribute favorably to patients' recovery. Total knee replacement is a common orthopedic surgery and is usually performed under spinal or general anesthesia, but the debate continues regarding which anesthesia method is better in terms of oxidative stress. Some studies have reported that general anesthesia, inhalation anesthetics, and propofol have an antioxidant effect on oxidative stress (6-10). Many oxidative stress markers are used to evaluate oksidative stress (11,12). Until 2014, thiol-disulfide homeostasis was only evaluated with a one-way measurement to determine whether thiol was increasing or decreasing. However, a method enabling the dual measurement of thiol and disulfide levels was developed. This new method is superior to older methods because it is faster and more accurate, is repeatable, and can be performed with both manual and colorimetric methods (13). The equilibrium between thiol and disulfide is measured by evaluating native thiol (-SH), dynamic disulfide (-S-S-), total thiol [(-SH) + (-S-S-)], and dynamic thiol-disulfide ratio (-SH/-S-S-) balance (13). Thiols react with free oxygen radicals to create disulfides in oxidative stress. With the oxidative stress caused by surgery, these compounds are consumed, resulting in decreases in total and native thiol levels. Thus, reduced native thiol-disulfide ratio and increased disulfide levels indicate oxidative stress. Oxidative stress occurs as a result of tissue damage, and surgical procedures are determined on the basis of thiol-disulfide balance (14). Our aim in this study was to use the new method mentioned above to evaluate the effects on oxidative stress of two different anesthesia techniques during TKR surgery.

MATERIAL and METHODS

Approval was obtained from ethics committee (protocol number E1/052/2019) before study initiation. The study was a randomized comparative trial conducted between November 2019 and April 2022 with a total of 56 patients who were scheduled to undergo TKR in the orthopedics clinic and were evaluated as American Society of Anesthesiology (ASA) risk class I or II. The patients were randomly assigned to one of two groups, the general anesthesia group (Group G; n=26) or the spinal anesthesia group (Group S; n=30). All study procedures were performed according to the institutional research committee and the ethical standards stated in the 1964 Declaration of Helsinki.

The patients' age, sex, body mass index (BMI), concomitant diseases, TQ time, pre- and postoperative hemodynamic values, preoperative and postoperative hour-24 hemoglobin levels, analgesics administered postoperatively, and any adverse reactions on postoperative day 1 were recorded. Exclusion criteria were inability to use either anesthesia method due to allergies and contraindications, undergoing revision TKR, undergoing bilateral TKR in the same session, using sedative and/or anxiolytic drugs, using antioxidant drugs and substances, and the presence of life-threatening systemic disease. Patients in both groups were given intravenous (IV) 0.03 mg kg^{-1} midazolam preoperatively.

In Group S, 500 mL of isotonic NaCl solution was administered by IV route before spinal anesthesia. The patients were placed in a seated position while their vital signs were being monitored. A lumbar puncture was then carried out using a 25-gauge needle inserted at the proper level while adhering to aseptic and antiseptic techniques. Bupivacaine (15 mg) was used for spinal anesthesia. The patient was returned to supine position and the level of anesthesia was assessed by pin prick test, after which the surgery was allowed to begin. In case of hypotension (25% below baseline) 5 or 10 mg ephedrine was administered; bradycardia was treated with 0.5 mg IV atropine; and oxygen support was provided via face mask if peripheral oxygen saturation fell below 91%.

In Group G, the patients were intubated with a suitable endotracheal tube after induction with IV 0.5-1 mg kg^{-1} lidocaine, 2 mg kg^{-1} propofol, 1 µg kg^{-1} fentanyl, 0.6 mg kg^{-1} rocuronium under standard monitoring, after which inhalation anesthesia with a 2% sevoflurane/40% oxygen/air mixture was started. Remifentanil infusion (1 µg kg^{-1} h^{-1}) was used as an analgesic during anesthesia maintenance. The patients were ventilated with a tidal volume of 6-8 mL kg^{-1} and end-tidal carbon di-

oxide was monitored. At the end of the operation, 2 mg kg^{-1} sugammadex was used for decurarization. In both groups, a pneumatic TQ was applied to the femoral region preoperatively. Pneumatic TQ pressure was adjusted to twice the measured systolic pressure. The TQ was released at the end of the surgery after the last skin suture and bandage were applied.

For postoperative analgesia, both groups received a total of 40 mg kg^{-1} day^{-1} IV paracetamol divided by 8-hour intervals and patient-controlled analgesia (PCA; Body Guard 575 Pain Manager) with tramadol (1 mg kg^{-1} loading dose followed by 14 mg basal infusion and 14 mg bolus per demand with 20-minute lockout time) until postoperative 24 hours. The patients' analgesia level was monitored using a visual analog scale (VAS) under the supervision of a nurse and the guidance of the lead investigator. Additional analgesics were administered to patients with a VAS score above 4. In both groups, blood samples (3 mL) were obtained by venipuncture in the non-catheterized arm before anesthesia (T1), 5 minutes after TQ release (T2), 40 minutes after TQ release (T3), and at postoperative 24 hours (T4). The blood was centrifuged for 5 minutes at 3000 rpm for 15 minutes and stored in a freezer (-80°C) until thiol/disulfide analyses.

Thiol-disulfide homeostasis tests were performed using the automated spectrophotometric assay described by Erel and Neselioglu (13). Briefly, disulfide bonds were first reduced to form free functional thiol groups with sodium borohydride. The unused sodium borohydride was removed by consuming with formaldehyde to prevent the reduction of DTNB (5.5'-dithiobis-(2-nitrobenzoic) acid). All thiol groups, including reduced and native thiol groups, were then measured using a DTNB solution with formaldehyde. After the determination of native and total thiols, disulfide amounts (half of the difference between total and native thiol levels), disulfide/total thiol ratios (SS/SH+SS), disulfide/native thiol percentage ratios (SS/SH), and native thiol/total thiol percentage ratios (SH/SH+SS) were calculated (13).

Statistical Analysis

Data analysis was performed using IBM SPSS version 25.0 (IBM Corp, Armonk, NY) statistical software. In addition to descriptive statistical methods (frequency, percentage, mean, standard deviation, median, range), the chi-square (χ^2) test was used to compare qualitative data. Normality of the data was evaluated using Kolmogorov-Smirnov test, skewness-kurtosis, and graphical methods (histogram, Q-Q plot, stem and leaf, boxplot). Independent-samples t-test was used to evaluate normally distributed quantitative data. Relationships between variables were evaluated using the Pearson correlation test. The level of statistical significance was accepted as α=0.05.

Power analyses were performed using G*Power 3.1.9.7 (Franz Faul, Universitat Kiel, Germany). Power analysis based on preanesthetic disulfide/native thiol ratio indicated that for n_1=30, n_2=26, α=0.05, and effect size (d)= 0.85, the study power was 88%.

Based on disulfide/total thiol ratio at 5 min after TQ release, study power with n_1=30, n_2=26, α=0.05, and effect size (d)= 0.86 was also 88%.

For native thiol/total thiol ratio at 40 min after TQ release, the study power was found to be 95% with n_1=30, n_2=26, α=0.05, and effect size (d)= 1.

RESULTS

There were 28 women and 2 men in Group S and 20 women and 6 men in Group G. There was no difference between the groups in terms of age, sex, BMI, ASA score, hemoglobin, fasting time, or comorbidities. The only significant difference between the groups was in the percentage of patients with chronic medication use p=0.036 (Table I).

Preanesthetic heart rate and recovery room VAS scores differed significantly between the groups (p<0.05). Patients in Group G had lower preanesthetic heart rate and higher recovery room VAS value. There were no significant differences in the other variables. Among the adverse reactions, postoperative nausea was the most common (n=5 in Group S, n=7 in Group G). Postanesthetic bradycardia and postoperative distended bladder were each observed in only one patient in Group S. In Group G, one patient experienced spasms while waking up from anesthesia (Table II).

In between-group comparisons, we detected statistically significant differences in native thiol at T2-T4, total thiol at T3 and T4, disulfide at T1-T3, disulfide/native thiol ratio at T1-T4, disulfide/total thiol ratio at T1-T4, and native thiol/total thiol ratio at T1-T4 (p<0.05). At all time points with significant differences, native thiol, total thiol, and native thiol/total thiol ratio were higher in Group G, while disulfide, disulfide/native thiol ratio, and disulfide/total thiol ratio were higher in Group S. There was no statistically significant difference between the groups in terms of blood glucose (glycemia) values (Table III).

In within-group comparisons of repeated measures, no significant differences were detected in disulfide, disulfide/native thiol ratio, disulfide/total thiol ratio, or native thiol/total thiol ratio values in Group G, while these values differed significantly in Group S (p<0.05).

Multiple comparison (post-hoc) tests showed that in Group S, disulfide level was significantly higher at T3 compared to T2 and T4 (p=0.002), disulfide/native thiol (p=0.007) and

Table I: Comparison of Demographic and Clinical Characteristics

		Group S (n=30)	Group G (n=26)	p
Gender (M/F)		2/28	6/20	0.127 [a]
Age (years)		67.6 ± 6.4	66.9 ± 6.7	0.723 [b]
BMI (kg m $^{-2}$)		32.2 ± 5.6	32.5 ± 9.3	0.911 [b]
ASA score	I	6 (20.0)	1 (3.8)	0.162 [a]
	II	24 (80)	25 (96.2)	
Comorbidity	Present	25 (83.3)	23 (88.5)	0.712 [a]
	HT	20 (66.7)	16 (61.5)	0.905 [a]
	DM	8 (26.7)	8 (30.8)	0.966 [a]
	Hypothyroidism	5 (16.7)	2 (7.7)	0.431 [a]
	CAD	4 (13.3)	2 (7.7)	0.675 [a]
	Asthma	2 (6.7)	3 (11.5)	0.655 [a]
	Other	8 (26.7)	12 (46.2)	0.216 [a]
Chronic medication use		18 (60.0)	23 (88.5)	**0.036** [a]
Hemoglobin (g dL^{-1})	Preoperative	12.9 ± 1.2	13.3 ± 1.4	0.290 [b]
	Postoperative	10.9 ± 1.6	11.4 ± 1.4	0.193 [b]
Fasting time (hours)		9.8 ± 2.0	10.8 ± 1.9	0.062 [b]

a: Chi-square test (n [%]), **b:** Independent-samples t-test (mean ± SD). **M:** Male, **F:** Female, **BMI:** Body Mass Index, **ASA:** American Society of Anesthesiologists, **HT:** Hypertension, **DM:** Diabetes mellitus, **CAD:** Coronary artery disease.

Table II: Comparison of Vital Signs and Operative Variables

		Group S (n=30)	Group G (n=26)	p
SpO_2 (%)	Preoperative	95.2 ± 2.6	96.8 ± 2.5	0.127 [b]
	Recovery Room	94.8 ± 2.4	94.5 ± 3.1	0.685 [b]
	Hour 24	93.8 ± 2.8	94.0 ± 3.0	0.761 [b]
MAP (mmHg)	Preoperative	108.9 ± 13.1	112.4 ± 11.8	0.298 [b]
	Postanesthetic	98.6 ± 14.6	96.3 ± 18.0	0.618 [b]
	Recovery	98.3 ± 13.2	101.3 ± 18.9	0.509 [b]
	Hour 24	87.9 ± 8.2	84.6 ± 9.1	0.155 [b]
Heart rate (beats min^{-1})	Preanesthetic	86.3 ± 20.8	75.2 ± 12.8	**0.023** [b]
	Postanesthetic	84.1 ± 23.1	74.9 ± 15.2	0.091 [b]
	Recovery	78.5 ± 19.0	75.0 ± 14.1	0.490 [b]
	Hour 24	85.8 ± 13.4	83.9 ± 12.0	0.587 [b]
TQ time (min)		92.5 ± 29.1	81.0 ± 26.5	0.133 [b]
VAS	Recovery	1.6 ± 1.8	6.2 ± 1.8	**<0.001** [b]
	Hour 24	2.5 ± 1.1	3.0 ± 2.1	0.232 [b]
Adverse reactions on postoperative day 1		7 (23.3)	8 (30.8)	0.746 [a]
Postoperative need for additional analgesic		16 (53.3)	18 (69.2)	0.347 [a]

a: Chi-square test (n [%]), **b:** Independent-samples t-test (mean ± SD), **SpO_2:** Oxygen saturation, **MAP:** Mean arterial pressure, **HR:** Heart rate, **TQ:** Tourniquet, **VAS:** Visual Analogue Scale.

Table III: Between-Group Comparisons of Glycemia and Thiol-Disulfide Parameters

		Group S (n=30)	Group G (n=26)	p
Native thiol (μmol L^{-1})	T1	260.6 ± 84.2	300.5 ± 77.1	0.072
	T2	194.2 ± 70.3	235.0 ± 74.4	**0.040**
	T3	188.1 ± 69.0	245.4 ± 77.8	**0.005**
	T4	237.7 ± 91.6	303.0 ± 82.4	**0.007**
Total thiol (μmol L^{-1})	T1	297.4 ± 82.2	329.5 ± 77.5	0.140
	T2	229.7 ± 73.5	263.0 ± 73.5	0.097
	T3	231.2 ± 68.4	272.8 ± 77.9	**0.038**
	T4	271.6 ± 93.6	333.8 ± 85.2	**0.013**
Disulfide (μmol L^{-1})	T1	18.4 ± 4.5	14.5 ± 4.8	**0.003**
	T2	17.8 ± 3.8	14.0 ± 4.8	**0.002**
	T3	21.6 ± 6.4	13.7 ± 5.3	**0.000**
	T4	17.0 ± 4.0	15.4 ± 3.9	0.150
Disulfide/native thiol ratio (%)	T1	8.2 ± 4.7	5.2 ± 2.5	**0.004**
	T2	10.1 ± 3.4	6.9 ± 4.2	**0.002**
	T3	13.4 ± 7.9	6.2 ± 3.7	**0.000**
	T4	9.0 ± 7.2	5.4 ± 1.9	**0.012**
Disulfide/total thiol ratio (%)	T1	6.8 ± 3.2	4.6 ± 1.9	**0.003**
	T2	8.3 ± 2.3	5.8 ± 2.9	**0.001**
	T3	10.0 ± 4.2	5.4 ± 2.6	**0.000**
	T4	7.2 ± 3.9	4.8 ± 1.5	**0.004**
Native thiol/total thiol ratio (%)	T1	86.3 ± 6.4	90.8 ± 3.8	**0.002**
	T2	83.4 ± 4.7	88.3 ± 5.9	**0.001**
	T3	79.9 ± 8.5	89.2 ± 5.3	**0.000**
	T4	85.6 ± 7.8	90.3 ± 2.9	**0.004**
Glycemia level (mg dL^{-1})	T1	119.1 ± 39.3	104.0 ± 22.3	0.085
	T2	130.2 ± 44.1	113.0 ± 22.5	0.077
	T3	145.8 ± 48.0	145.3 ± 27.1	0.963
	T4	198.0 ± 81.7	178.3 ± 56.8	0.319

Independent-samples t-test (mean ± SD). **T1:** Preanesthetic, **T2:** 5 minutes after tourniquet release, **T3:** 40 minutes after the tourniquet release, **T4:** Postoperative hour 24.

disulfide/total thiol ratios (p=0.001) were higher at T3 than T1, and native thiol/total thiol ratio was lower at T3 than T1 (p=0.001) (Table IV).

DISCUSSION

Our study showed that general anesthesia had positive effects on oxidative stress compared to spinal anesthesia. This effect was demonstrated as higher levels of native thiol, total thiol, and native thiol/total thiol ratio and lower disulfide, disulfide/native thiol ratio, and disulfide/total thiol ratio at all time points.

One study compared the effect of general and epidural anesthesia on stress hormones in major lower extremity surgeries but detected no significant differences between the two groups (15). Akin et al. investigated the effect of general and spinal anesthesia on maternal/neonatal thiol-disulfide homeostasis in pregnant women who had cesarean delivery and found that there were increases in postoperative native thiol, total thiol, disulfide/total thiol, and disulfide levels with general anesthesia compared to spinal anesthesia, suggesting that general anesthesia increased oxidative stress in cesarean section (16). Omur et al. examined the ischemia-modified albumin (IMA) levels in maternal and cord blood by dividing 51 healthy pregnant women undergoing cesarean section into the general and combined spinal-epidural anesthesia groups and found that both IMA and IMA/albumin ratios were significantly higher in patients in the general anesthesia group at

Table IV: Within-Group Comparisons of Thiol-Disulfide Parameters

		Group S (n=30)	Group G (n=26)
Disulfide (μmol L^{-1})	T1	18.4 ± 4.5	14.5 ± 4.8
	T2	17.8 ± 3.8	14.0 ± 4.8
	T3	21.6 ± 6.4	13.7 ± 5.3
	T4	17.0 ± 4.0	15.4 ± 3.9
p		**0.002**	0.457
Difference		T3 vs. T2, T4	--
Disulfide/native thiol ratio (%)	T1	8.2 ± 4.7	5.2 ± 2.5
	T2	10.1 ± 3.4	6.9 ± 4.2
	T3	13.4 ± 7.9	6.2 ± 3.7
	T4	9.0 ± 7.2	5.4 ± 1.9
p		**0.007**	0.063
Difference		T1 vs. T3	--
Disulfide/total thiol ratio (%)	T1	6.8 ± 3.2	4.6 ± 1.9
	T2	8.3 ± 2.3	5.8 ± 2.9
	T3	10.0 ± 4.2	5.4 ± 2.6
	T4	7.2 ± 3.9	4.8 ± 1.5
p		**0.001**	0.068
Difference		T1 vs.T3	--
Native thiol/total thiol ratio (%)	T1	86.3 ± 6.4	90.8 ± 3.8
	T2	83.4 ± 4.7	88.3 ± 5.9
	T3	79.9 ± 8.5	89.2 ± 5.3
	T4	85.6 ± 7.8	90.3 ± 2.9
p		**0.001**	0.069
Difference		T1 vs.T3	--

Repeated-measures ANOVA (mean ± SD). **T1:** Preanesthetic, **T2:** 5 minutes after tourniquet release, **T3:** 40 minutes after the tourniquet release, **T4:** Postoperative hour 24.

postoperative 30 minutes compared to the preoperative period, while there was no difference in the combined spinal-epidural anesthesia group (17). In a study comparing general and spinal anesthesia in terms of oxidative stress in gynecological laparoscopy, no significant differences were detected but spinal anesthesia was found to be safe (18). Mas et al. compared general anesthesia and spinal anesthesia in terms of oxidative stress parameters (F2-isoprostane and isophorone) in patients undergoing knee replacement surgery and concluded that general anesthesia increased oxidative stress in direct proportion to increased oxygen concentration (19). Karabayırlı et al. compared general and regional anesthesia in elective cesarean section and found that general anesthesia was more advantageous than regional anesthesia in terms of oxidative stress (20). We also found that general anesthesia was more advantageous in terms of oxidative stress parameters.

Several studies have shown that pain reduction reduces oxidative stress (21, 22). One study showed that peripheral and central sensitization caused oxidative stress and hyperalgesia can also cause oxidative stress (23). Oksuz et al. compared oxidative stress parameters in patients who were given general anesthesia and those who received interscalene block during shoulder arthroscopy and found that postoperative thiol levels were lower and disulfide levels were higher in the general anesthesia group. Therefore, the authors concluded that general anesthesia increases oxidative stress, that this was directly proportional to VAS scores, and pain increases oxidative stress (24).

In our study, we found that postoperative VAS scores were significantly higher in the general anesthesia group compared to the spinal anesthesia group, but this difference did not persist at postoperative 24 hours. However, native thiol, total thiol, and native thiol/total thiol ratio were higher in the general anesthesia group at all time points. In contrast, disulfide, disulfide/native thiol ratio, and disulfide/total thiol ratio were significantly higher in the spinal anesthesia group at all time points. This suggests that general anesthesia reduces oxidative stress. In the study by Oksuz et al., it was observed that MAP values were higher in the general anesthesia group compared to the interscalene block group only in the postoperative follow-up and was lower in all other times. This was thought to be due to the higher level of pain in the general anesthesia group (24). Major changes in blood pressure can affect oxidative stress parameters. In one study, acute hypertension was reported to increase cerebral oxidative stress (25). In our study, we observed no statistical difference in MAP at any recorded time point.

Allaouchiche et al. found that propofol and sevoflurane had more favorable effects in a mechanically ventilated pig model (6). In another study, sevoflurane was found to have more favorable effects than other inhalation agents in terms of oxidative stress in elective cesarean deliveries (7). In a study conducted at the cellular level, it was shown that antioxidant defense mechanisms increased and oxidative stress decreased in the red blood cells of people who received sevoflurane (8). In a study of patients undergoing laparoscopic surgery, desflurane was shown to increase plasma malondialdehyde (MDA) and protein carbonyl content and decrease -SH level compared to sevoflurane (9). Aremu et al. observed in their study that spinal and general anesthesia had different effects on inflammatory cytokines and oxidative stress in orthopedic patients (26). A study of patients undergoing hip replacement

surgery showed that general anesthesia combined with epidural anesthesia was more beneficial in terms of oxidative stress compared to epidural or general anesthesia alone (27). In another study, the use of remifentanil in patients undergoing laparoscopic surgery for colon cancer was shown to reduce oxidative stress postoperatively (10).

Turan et al. found that the use of propofol restored antioxidant enzyme levels and inhibited lipid peroxidation in extremity surgeries requiring TQ application (28). In a review, it was stated that propofol had a protective effect on oxidative and inflammatory markers of TQ-induced ischemia-reperfusion injury in TKR surgery. In the same review, it was concluded that sevoflurane and halothane had less potent antioxidant properties than propofol, so spinal anesthesia and low-dose propofol infusion would be more appropriate in TKR (29). Various other studies have shown that some anesthetic agents can reduce elevations in the ischemia-reperfusion markers resulting from the TQ used in orthopedic surgeries (30). We also evaluated TQ time because of its potential effect on oxidative stress, but observed no difference.

However, our study had some limitations. Group G and Group S had statistically different disulfide, disulfide/native thiol ratio, disulfide/total thiol ratio, and native thiol/total thiol ratio at T1 (i.e., at baseline). To determine the cause of these differences, we also compared these four parameters within the groups and found that there were significant differences in the spinal anesthesia group at 40 minutes after TQ release. We believe that the oxidative stress caused by the TQ was significant in the spinal anesthesia group, while there was no significant difference from baseline in the general anesthesia group because of its favorable effect on oxidative stress. In addition, although our groups did not differ significantly in this regard, the high BMI and age values specific to this disease and surgery group may have affected the results of our study. We noted a significant difference between the groups in the proportion of patients with chronic medication use. However, sufficient data could not be obtained regarding the positive or negative effects on oxidative stress parameters in the preoperative period.

CONCLUSION

In this study we observed positive effects of general anesthesia on TQ- and surgery-induced oxidative stress in TKR procedures and we attribute these effects to the use of propofol, sevoflurane, and remifentanil. Because the general anesthesia group had higher native thiol, total thiol and native thiol/total thiol ratio and lower disulfide, disulfide/native thiol ratio and disulfide/total thiol ratio at all time points compared to the spinal anesthesia group. Further studies can be conducted to investigate the relationship between oxidative stress and TQ use, general anesthesia, and spinal anesthesia.

AUTHOR CONTRIBUTIONS

Conception or design of the work: EMS, SMA
Data collection: EMS
Data analysis and interpretation: EMS
Drafting the article: EMS, OE, SN
Critical revision of the article: NM, AF
The author (EMS, SMA) reviewed the results and approved the final version of the manuscript.

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