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The Effect of Dexmedetomidine and Propofol on Oxidative Stress Parameters during Lower Extremity Surgery: A Prospective Randomized Trial

Safinaz Karabayırlı[1], Ismail Uras[2], Cemile Koca[3], Merve Ergin[4], Ruveyda Irem Demircioglu[5] and Bunyamin Muslu[5]

[1]*Assistant professor, Department of Anesthesiology, Faculty of Medicine, Turgut Ozal University, Ankara, Turkey*

[2]*Assistant professor, Department of Orthopaedic Surgery, Faculty of Medicine, Turgut Ozal University, Ankara, Turkey*

[3]*Associate professor, Department of Clinical Biochemistry, Faculty of Medicine, Yıldırım Beyazıt University, Ankara, Turkey*

[4]*MD, Department of Clinical Biochemistry, Faculty of Medicine, Yıldırım Beyazıt University, Ankara, Turkey*

[5]*Associate professor, Department of Anesthesiology, Faculty of Medicine, Turgut Ozal University, Ankara, Turkey*

***Corresponding author:** *Safinaz Karabayırlı, Department of Anesthesiology, Faculty of Medicine, Turgut Ozal University, Alparslan Turkes Caddesi, No: 57, 06520 Yenimahalle, Ankara, Turkey, Tel: +90 3122035170, E-mail: drsafinaz@yahoo.com*

Abstract

Background: This study aims to compare the impact of sedation, continuous dexmedetomidine and propofol infusion, to oxidative stress that occurred as a result of tourniquet-induced ischemia reperfusion (IR) during lower extremity surgery.

Material & Methods: All patients were administered combined spinoepidural anesthesia; Group D received infusion of 1μg kg^{-} dexmedetomidine for 10 minutes and 0.5μg $kg^{-}h^{-}$ infusion, Group P was administered 0.2 mg kg^{-}propofol following bolus 2 mg $kg^{-}min^{-}$. At baseline, 20 minutes and two hours after the tourniquet was released, plasma total antioxidant status (TAS), total oxidant status (TOS), paraoxonase (PON), stimulated paraoxonase (SPON), arylesterase, ceruloplasmin, myeloperoxidase (MPO), ischemia modified albumin (IMA) and advanced oxidation protein products (AOPP) levels were analyzed.

Results: In Group D, ceruloplasmin values taken post tourniquet release were lower compared to the baseline values ($p = 0.02$ and 0.008, respectively). As for Group P, a decrease in the TAS and TOS values was recorded two hours after the tourniquets were released (in both $p = 0.008$). No differences were found in other markers of oxidative stress during intra-group comparisons ($p > 0.05$).

Conclusion: The study concluded that administration of propofol and dexmedetomidine sedation during lower extremity surgery had similar effects on oxidative stress caused by tourniquet-induced IR.

Keywords

Dexmedetomidine, Ischemia-reperfusion, Oxidative stress, Propofol, Tourniquet

Introduction

Tourniquets are routinely applied during lower extremity surgery in order to reduce bleeding during surgery, provide better surgical conditions and consequently to shorten the duration of the operation. However, an inflammatory response is often activated by tourniquet application, leading to prolonged ischemia and reperfusion; consequently, organ damage such as acute lung injury may occur [1-3]. Muscular ischemia causes hypoxic cellular changes and anaerobic glycolysis, and its neutrophil activation with reperfusion causes the formation of oxygen radicals and the release of vasoactive mediators [4].

In order to decrease or eliminate the negative effects related to the use of tourniquets, the use of various medicaments were tested, such as: inhalation anesthetics, intravenous general anesthetics, vitamin E, vitamin C, N acetyl cysteine (NAC) and ischemic preconditioning applications [5-13]. Regarding ischemic preconditioning application and oxidative stress parameters after ischemia-reperfusion (IR), positive results were obtained for pulmonary dysfunction [5-13]. However, it may not always be possible to perform ischemic preconditioning when applying a tourniquet, such as in cases of war injuries or severe bleeding [14]. Experimental and clinical studies have shown that volatile and IV anesthetic can be effective for ischemia-reperfusion. Animal and human studies have also reported that the use of propofol during the anesthesia application minimizes ischemia-reperfusion injury and reduces oxidative changes like lipid peroxidation [5-10].

Dexmedetomidine is a α_2 and is used for sedation purposes in patients to whom regional anesthesia is applied. Dexmedetomidine suppresses the tourniquet-induced hyperdynamic response during

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lower extremity surgery [15]. A positive impact on IR has been reported in animal and human studies [16-20]. Research has been conducted to determine whether dexmedetomidine has effects on lower extremity surgery, but conflicting results have been reported [19,20]. The current study compared the impact of sedation application using continuous dexmedetomidine and propofol infusion on oxidative stress that occurred as a result of IR, where a tourniquet applied during lower extremity surgery in patients who received regional anesthesia.

Method

After ethics committee approval was granted by the Fatih University Faculty of Medicine Ethic Committee (no: B30 2 FTU 0 00 00/2480, Chairperson Prof. S Dane) patients who wished to join this research were informed about the study and provided voluntary written consent. This study was designed as a prospective, randomized cohort study. A total of 50 patients between the ages of 18 and 75, ASA I-III, who planned to undergo elective lower extremity surgery with tourniquet application period more than 60 min into the operation were included in this study. Several patients were excluded: those suffering from vascular disease, cardiovascular and respiratory diseases or liver and renal dysfunction; those with pulmonary embolisms or deep vein thrombosis; those receiving antioxidant, anti-inflammatory treatment and preoperative oxygen therapy; and those to whom intramedullary nailing was applied. All patients received 1000 ml Ringer lactate infusion before the operation. No premedication was given, and after the patient was taken into the operation room, standard monitoring with DII and V5 electrocardiography, pulse oximetry and noninvasive blood pressure was applied.

After sterilization for combined spin epidural anesthesia was provided to patients in the sitting position, the epidural space was detected using the hanging drop technique with an 18-gauge Tuohy needle (Espocan® +Docking System+Perifix®, Brown, Germany). By using the needle-through-needle technique, 15 mg (3 ml 0.5%) heavy bupivacaine and 20 µg fentanyl were injected with a 27-gauge pencil point spinal needle into the intrathecal space. After the epidural space was expanded with 3 ml SF, a 20-gauge epidural catheter was inserted into the epidural space and secured. The patients were brought to the supine position and sensorial block level was controlled with a pinprick test. After it was observed that a 3rd level motor block had formed according to the T10 sensory block and Bromage scale, surgical procedures were allowed to start.

The number of patients enrolled in this study was determined based on our preliminary study and a power of 80% and significant difference for OSI value amount three groups with a significance level of 5%. Sample size was calculated as 12 patients for each group. The patients were randomly divided by computer into two groups before the start of the operation. Drug dose used in this study was determined based on previous studies [8-10,19,20]. In group dexmedotomidine (Group D) (n = 25), dexmedetomidine 1µg kg^{-} was infused intravenously (IV) for 10 minutes, followed by a continuous infusion of 0.5µg $kg^{-}h^{-}$ during the operation for sedation. In group propofol (Group P) (n = 25), a 0.2 mg/kg bolus dose of propofol was administered and 2 mg $kg^{-}min^{-}$ infusion was applied during the operation. All the patients were administered oxygen with a 2 liter/min irreversible nasal mask in order to prevent the development of desaturation caused by sedation during surgery. The patients were monitored during the operation at baseline, after 5 minutes and at subsequent 10 min intervals, for heart rate (HR), oxygen saturation (SpO_2) and mean arterial blood pressure (MAP), and sensorial and motor block. The durations of the anesthesia, surgery, and tourniquet application were recorded.

Two venous blood samples were taken from all patients before tourniquet application (t1), 20 minutes after the tourniquet was released (t2) and two hours after the tourniquet was released (t3). Venous blood gases were assessed with the first blood samples. The second blood samples were centrifuged at 3000 cycle for 10 minutes and were stored at -80 degrees, until the plasma total antioxidant status (TAS), total oxidant status (TOS), paraoxonase (PON), stimulated paraoxonase (SPON), arylesterase, ceruloplasmin, myeloperoxidase (MPO), ischemia modified albumin (IMA) and advanced oxidation protein product levels (AOPP) were analyzed.

Determination of Oxidative and Antioxidative Stress Markers

PON and arylesterase activities were measured using commercially available kits (RelassayR, Gaziantep, Turkey). PON activity measurements were performed in the absence (basal activity) and presence (salt-stimulated activity, stimulated paraoxonase (SPON)) of NaCl. PON activity was expressed as U/L serum[21].

Phenylacetate was used as a substrate to measure arylesterase activity. One unit of arylesterase activity was defined as 1 µmol phenol generated/min under the above conditions and expressed as KU/L serum [22].

The TOS of plasma was measured using the novel automated colorimetric method described by Erel [23]. The assay is calibrated with hydrogenperoxide, and the results are expressed in terms of micromolar hydrogenperoxide equivalent per liter (µmol H_2O_2 Eqv./L) [23].

Serum TAS was measured using the novel automated colorimetric measurement method developed by Erel. The results are expressed as milimolar trolox equivalent per liter [24].

For calculation of oxidative stress index (OSI), the resulting unit of TAS was converted to µmol/L, and the OSI value was calculated according to the following formula: OSI (arbitrary unit) = TOS (µmol H_2O_2 equivalent/L) / TAS (µmol Trolox equivalent/L) [25].

The quantification of advanced oxidation protein products (AOPP) in plasma used the method described by Witko-Sarsat et al. [26] AOPP concentrations were expressed in µmol/liter of chloramine-T equivalents.

Serum myeloperoxidase (MPO) activity was determined by a modification of the o-dianisidine method. MPO activity was expressed in units per liter serum [27].

Ceruloplasmin levels were measured as described automated, colorimetric, and based on the enzymatic oxidation of ferrous ion to ferric ion. The results were expressed in milligrams per deciliter, and the precision of this assay is lower than 3% [28].

Reduced cobalt to albumin-binding capacity (IMA level) was measured using the rapid and colorimetric method developed by Bar-Or et al. and the results were expressed as absorbance units (ABSU) [29].

Statistical Analysis

All statistical calculations were performed using Statistical Package for the Social Sciences (SPSS) software for Windows, version 20 (SPSS Inc., Chicago, IL, USA). Normal distribution of the collected data was tested using the Shapiro-Wilk test. A Student's t-test was used for analysis of the normally distributed parameters, and Mann-Whitney-U was used to evaluate the non-normally distributed parameters. Categories were described using frequency distributions and compared by group using a chi- square test. Friedman's test was used for statistical comparisons of in-group variables, and the Wilcoxon test with Bonferroni error correction was used for multiple comparisons. Values were presented as mean ± SD or median (25-75% per) in the manuscript, figures and tables. $P < 0.05$ was accepted as statistically significant. $P < 0.017$ was considered statistically significant with Bonferroni correction.

Results

A total of 50 patients who fulfilled the inclusion criteria were included in the study. Four patients from the dexmedetomidine group and three patients from the propofol group were excluded from the

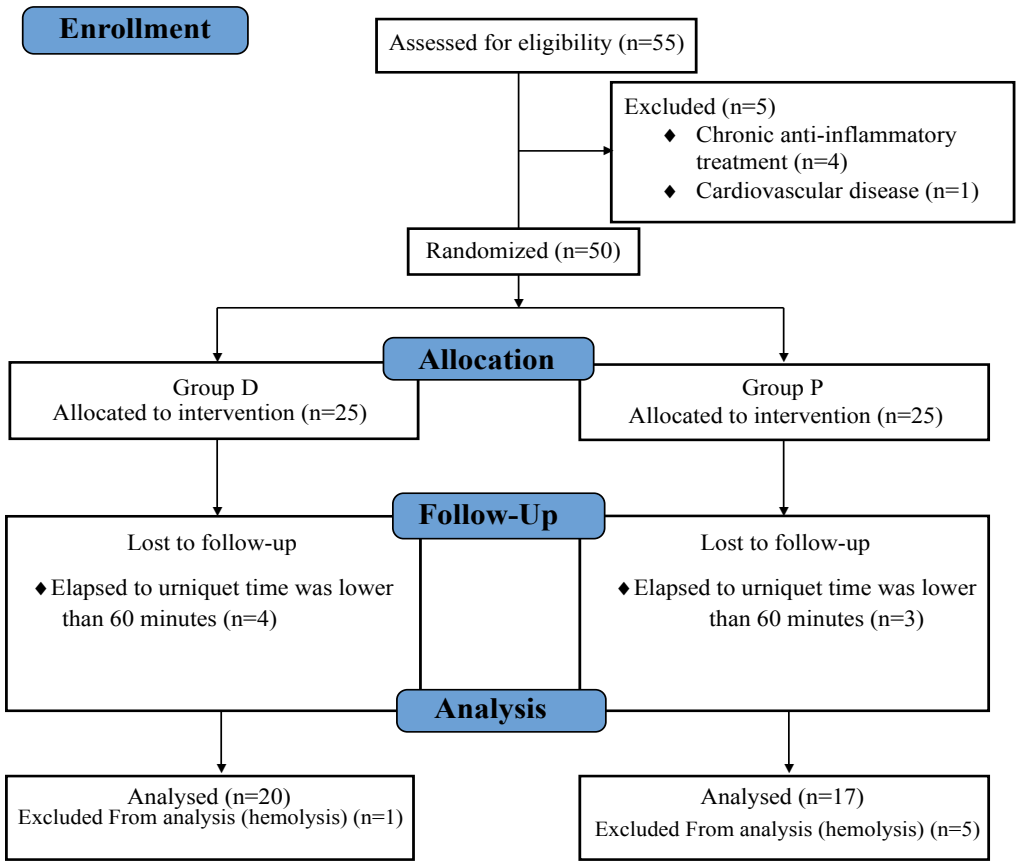

Figure 1: Flow diagram

Table 1: Demographic and operative data in groups

	Group D (n= 20)	Group P (n= 17)	P
Age (year)	56.6 ± 11.2	55.4 ± 12.9	0.655
Height (cm)	163.4 ± 6.9	163.5 ± 8.3	0.737
Weight (kg)	83.7 ± 13.3	85.2 ± 12.3	0.835
Body mass index	30.6 ± 6.1	31.4 ± 4.4	0.236
Gender male/female (n)	6/14	6/11	0.732
Duration of anesthesia (min)	134.7 ± 36.9	128 ± 28.3	0.744
Duration of surgery (min)	115.2 ± 36.8	102.9 ± 28.8	0.359
Duration of total tourniquet time(min)	97.5 ± 28.7	93.5 ± 30.1	0.598
Chronic disorders (n)			
Diabetes mellitus	3/17	3/14	0.828
Hypertension	10/10	4/13	0.098
Surgery distribution (n)			
(TKR/ AKS/ STF / ET)	9/10/0/1	11/5/1/0	0.302

Data presented as mean ± SD and number of patients.

*: P<0. 05 was accepted statistically significant. (TKR: Total Knee Replacement, AKS: Arthroscopic Knee Surgery, STF: Surgical Treatment of Fracture, ET: *Excision* of *Tumor)*

study as the elapsed tourniquet time was lower than 60 minutes. A total of six patients from each group were excluded from the study as the blood samples taken from these patients could not be studied due to hemolysis. Blood samples were received from 20 patients from the dexmedetomidine group and from 17 patients in the propofol group, and TAS, TOS, PON, SPON, arylesterase, MPO, ceruloplasmin, AOPP and IMA levels were studied (Figure 1). Demographic and operative data were no difference between the groups (Table 1).

During the follow-ups carried out after the operation, no statistically significant differences between the groups in terms of MAP, HR and SpO_2 were determined ($p > 0.05$). In both groups the SpO_2 values of the patients during the operation did not fall below 90%. When evaluating venous blood gas values, the pH values in the propofol group both at baseline and 20 minutes after the tourniquet was released, as well as overall $PvCO_2$, PvO_2 and Sa values, were observed to be significantly lower compared to the dexmedetomidine group (Table 2). Between-group evaluations showed that baseline values of TOS measurements and OSI calculations were significantly higher in the propofol group (respectively $p = 0.026$ and 0.028). PON, SPON and AOPP values were higher in the propofol group 20 minutes after the tourniquet was released (Table 3). Evaluations of intra-group measurement times (t1, t2, t3) in the dexmedetomidine group for TAS, PON, SPON, ceruloplasmin, IMA and AOPP revealed significant differences; however, in doublet measurement time evaluation, TAS, PON, SPON, IMA and AOPP measurements, no significant difference was identified with Bonferroni correction. In the t1-t2 and t1-t3 comparisons of ceruloplasmin using Bonferroni correction, a significant decrease was determined in Group D ($p = 0.02$ and 0.008, respectively) (Figure 2). The evaluations carried out between the measurement times (t1, t2, t3) in the propofol group showed significant differences in TAS and TOS measurements (respectively, $p = 0.022$ and 0.039). For doublet comparison of measurement time, it was observed that t1-t3 comparisons of TAS and TOS values showed a significant decrease with Bonferroni correction (in both $p = 0.008$) (Figure 3). When comparing intra-group measurement times in the propofol group, no differences were determined in other oxidative stress parameters that were assessed (Figure 2).

Discussion

This study examined the effects of dexmedetomidine and propofol sedation practices on the oxidative stress parameters in patients who underwent lower extremity surgery with regional anesthesia and to

Table 2: Venous blood gas analysis of patients in groups

		Group D (n= 20)	Group P (n= 17)	P
pH				
	t1	7.38 ± 0.27	7.35 ± 0.04	0.024*
	t2	7.34 ± 0.24	7.30 ± 0.06	0.015
	t3	7.32 ± 0.45	7.34 ± 0.03	0.376
$PvCO_2$				
	t1	41.50 ± 4.35	42.60 ± 4.92	0.457
	t2	42.09 ± 3.73	48.70 ± 6.22	0.001*
	t3	45.17 ± 6.04	45.17 ± 6.04	0.750
PvO_2				
	t1	36.05 ± 13.3	30.58 ± 7.7	0.146
	t2	51.90 ± 17.8	29.05 ± 9.0	0.001*
	t3	38.25 ± 21.6	31.41 ± 10.7	0.245
Sa				
	t1	55.2 ± 18.0	52.7 ± 16.9	0.669
	t2	75.3 ± 17.0	46.8 ± 17.8	0.001*
	t3	48.6 ± 21.7	52.1 ± 22.8	0.638
Lactate				
	t1	1.4 ± 0.6	1.6 ± 0.4	0.202
	t2	1.6 ± 0.7	2.0 ± 0.5	0.069
	t3	1.4 ± 0.5	1.6 ± 0.4	0.189
HCO_3				
	t1	23.4 ± 1.4	23.0 ± 1.7	0.544
	t2	21.8 ± 1.3	20.9 ± 2.2	0.175
	t3	21.7 ± 1.7	21.8 ± 1.0	0.774

Data presented as mean ± SD.

*: P < 0. 05 was accepted statistically significant. t1: Baseline, t2: 20th minutes after tourniquet release, t3: 2 hour after tourniquet release

Table 3: Plasma oxidant and antioxidant levels at the measurement time in groups

		Group D (n= 20)	Group P (n= 17)	P
TAS				
	t1	1.86(1.61-1.97)	1.91(1.73-2.16)	0.497
	t2	1.67(1.51-1.99)	1.68(1.57-1.83)	0.311
	t3	1.74(1.64-1.90)	1.69(1.57-1.83)**	0.404
TOS				
	t1	2.70(1.91-5.01)	5.18(3.16-20.56)	0.026*
	t2	2.41(1.50-5.07)	2.34(1.06-4.63)	0.775
	t3	2.50(1.58-5.04)	2.17(1.26-4.10)**	0.422
OSI				
	t1	0.14(0.11-0.22)	0.39(0.14-1.31)	0.028*
	t2	0.14(0.09-0.32)	0.12(0.07-0.23)	0.577
	t3	0.13(0.09-0.27)	0.11(0.07-0.24)	0.422
PON				
	t1	108(72-225)	185(131-277)	0.104
	t2	108(69-157)	174(121-275)	0.012*
	t3	87(71-167)	235(94-265)	0.67
SPON				
	t1	290(188-674)	567(229-829)	0.220
	t2	299(178-485)	542(394-840)	0.010*
	t3	239(176-515)	727(268-810)	0.580
Arylesterase				
	t1	145(72-175)	125(94-179)	0.775
	t2	82(64-151)	104(68-159)	0.357
	t3	130(88-175)	111(40-185)	0.888
Ceruloplasmin				
	t1	17,8(15,1-22,3)	16.6(12.0-20.8)	0.232
	t2	13.3(10,6-16.0)**	15.5(11.3-19.2)	0.390
	t3	12.6(11.2-18.0)**	13.9(10.6-18.6)	0.814
MPO				
	t1	99(73-150)	113(55-160)	0.821
	t2	72(56-148)	105(52-167)	0.684
	t3	81(57-135)	82(63-161)	0.276
IMA				
	t1	0.62(0.54-0.66)	0.62(0.57-0.66)	0.916
	t2	0.65(0.64-0.69)	0.66(0.60-0.72)	0.937
	t3	0.63(0.57-0.69)	0.63(0.60-0.67)	0.311
AAOP				
	t1	33.4(24.7-51.2)	41.9(34.3-80.8)	0.311
	t2	25.3(18.4-38.8)	35.1(24.4-56.7)	0.028*
	t3	26.4(22.0-42.2)	30.3(20.8-52.5)	0.539

Data presented as median (min-max).

*: P < 0. 05 was accepted statistically significant. **: P < 0.017 was considered statistically significant with Bonferroni corrections for multiple comparisons. t1: Baseline, t2: 20th minutes after tourniquet release, t3: 2 hour after tourniquet release.

whom a tourniquet was applied. The basal TOS and OSI values and the PON and SPON values 20 minutes after the tourniquet was released were found to be higher in the propofol group. In intra-group comparisons, only the values of ceruloplasmin were found to decrease in Group D, and values of TAS and TOS decreased two hours after tourniquet release in Group P. However, there were no differences determined between the other oxidative stress parameter values in between-group or intra-group comparisons. In Group D $PvCO_2$, PvO_2 and Sa values of venous blood gases after 20 minute the turnique (t2) release were lower than group P. We did not observe any desaturation in both group. As the t2 time denoted the early postoperative period. The reason of this finding is longer sedation time of dexmedetomidine than propofol. Propofol contains a phenolic hydroxyl group, and the structure resembles that of a-tocopherol (vitamin E), a natural antioxidant [30] The antioxidant effects of this agent have been demonstrated in many animal and human studies where a tourniquet has been applied [5-10]. Budic et al. [5] investigated the total antioxidant capacity in extremity surgery in children, concluding that TIVA application administered with the use of propofol decreases post-tourniquet IR when compared to the application of inhalation or regional anesthesia. Even unrelated studies, such as those that researched the effects of sevoflurane and propofol anesthesia on oxidative stress in total knee arthroplasty and total knee replacement operations in which a tourniquet was applied, reached conclusions that support the antioxidant effects of propofol [6-7].

The use of propofol has been demonstrated not only to have positive effects on the application of anesthesia but also on oxidative stress when simultaneously applied in the sedation dose. It is hypothesized that the use of propofol for sedation at the time of tourniquet application would reduce lipid peroxidation and restore antioxidant enzyme levels [8-10]. A spinal anesthesia study where propofol infusion was applied in similar doses to the current study (2 mg kg^{-} bolus followed by infusion at a rate of 0.2 mg kg^{-} h^{-}) and compared to midazolam sedation observed lower amounts of tourniquet-induced free oxygen radical production in the propofol group [9]. The findings of the current study are similar to the results above. In this study, a decrease in TAS was observed two hours after the release of the tourniquet in the propofol group, and no significant changes were noted in the other parameters in terms of baseline values.

Even though dexmedetomidine entered clinical use with the purpose of sedation for intensive care patients, it is a selective α-2 agonist agent, the widespread use of which is also increasing in

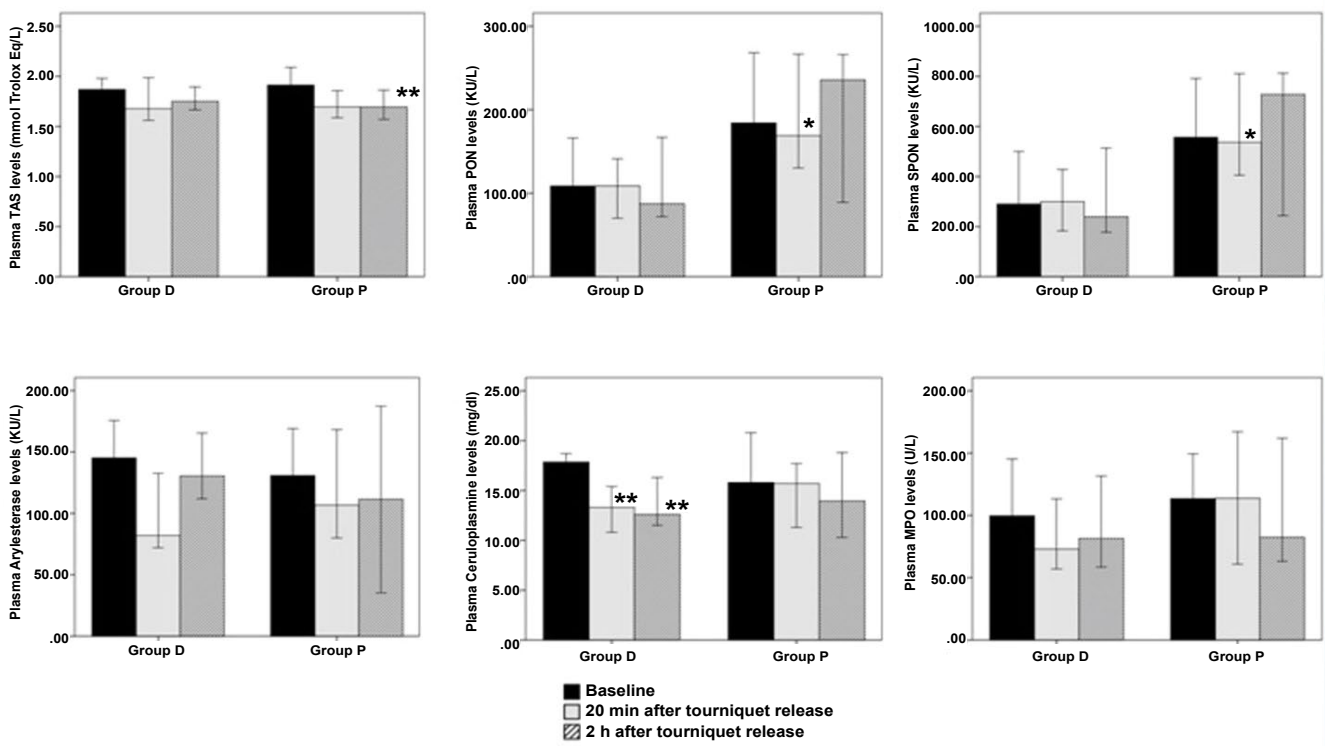

Figure 2: Baseline and after tourniquet release plasma levels antioxidant markers in groups. Error bars: 95% CI

*: P < 0. 05 was accepted statistically significant.

**: P < 0.017 was considered statistically significant with Bonferroni corrections for multiple comparisons.

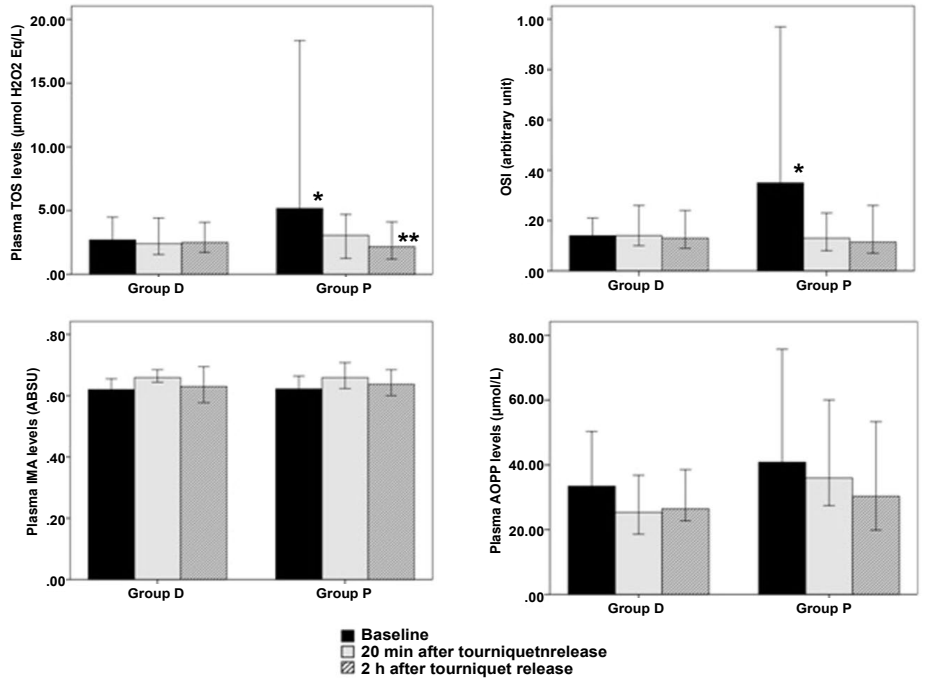

Figure 3: Baseline and after tourniquet release plasma levels of oxidant markers in groups. Error bars: 95% CI

*: P < 0. 05 was accepted statistically significant.

**: P < 0.017 was considered statistically significant with Bonferroni corrections for multiple comparisons.

anesthesia applications. In the experimental testicular torsion study of Unsal et al. [16], characteristics similar to the positive effects of propofol on histopathological and oxidative stress were demonstrated with dexmedetomidine. A related animal study was demonstrated the positive effects of dexmedetomidine on the MDA and TAS values as well as on apoptosis [17] In addition to the positive effect of dexmedetomidine on patients who underwent tourniquet application, Yağmurdur et al. [19] stated that these effects reduce the prevalence of ischemia-reperfusion injuries. In this study, which investigated the effects of dexmedetomidine in extremity surgery when a tourniquet was applied, 40 patients were administered a brachial block 1µg kg^{-} infusion over 10 minutes followed by 5µ kg^{-} h^{-} infusion. 15 minutes after the tourniquet was released, plasma hypoxanthin and MDA levels were found to be significantly lower

in the dexmedetomidine group compared to the control group [19]. According to their results, Yağmurdur et al. [19] suggested that the use of dexmedetomidine might be beneficial in suppressing lipid peroxidation in surgeries with a possibility of IR, although Bostankol et al. [20] concluded that additional application of dexmedetomidine infusion to general anesthesia does not reduce tourniquet-induced IR. In the current study, however, no negative effects on oxidative stress were observed across all parameters, excluding ceruloplasmin, when the baseline values were compared with the measurements made after the tourniquet was released. Taking this condition into account, the use of dexmedetomidine for sedation purposes can be considered to have positive effects on oxidative stress in tourniquet-induced IR.

The main limitation of this study is the absence of control group. Firstly we decided to add a control group which were not sedated (placebo), but than intraoperatively patients comfort were poor. So we canceled the control group. Since there were many studies with propofol we compared the propofol with other agent as dexmedetomidine which was less studied before.

In addition to TAS, TOS and OSI values, the current study also examined the measurement of parameters such as PON, SPON, ceruloplasmin, IMA and AAOP to determine levels of oxidative stress. However, no differences were determined among those parameters between the groups apart from the PON, SPON and AOPP values which were measured 20 minutes after the tourniquet was released. In intra-group comparisons in the propofol group, decreases in TAS and TOS values were recorded two hours after the tourniquet was released as compared to baseline values. Ceruloplasmin was reduced in Group D in intra-group comparisons at 20 minutes and two hours after the tourniquet was released. In the previous study a correlation between ceruloplasmin, ceruloplasmin oxidase activity and lower limb ischemia level was found [31]. But in this study the other oxidative and anti-oxidative markers which were specific for ischemia were evaluated no changes were detected at the intra-group comparisons in both groups. These findings suggest that the dexmedetomidine and propofol sedation practices have similar effects on oxidative stress. In conclusion, the application of sedation using propofol and dexmedetomidine in lower extremity surgery has similar effects on oxidative stress as related to tourniquet-induced IR.

Declaration Of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Approval Ethics Committee

Local Clinical Research Ethics Committee of the Fatih University.

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