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SCIENTIFIC ARTICLE

Effects of various anesthesia maintenance on serum levels of selenium, copper, zinc, iron and antioxidant capacity

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Abstract

Background and objectives: In this study, we aimed to investigate the effects of sevoflurane, desflurane and propofol maintenances on serum levels of selenium, copper, zinc, iron, malondialdehyde, and glutathion peroxidase measurements, and antioxidant capacity.

Methods: 60 patients scheduled for unilateral lower extremity surgery which would be performed with tourniquet under general anesthesia were divided into three groups. Blood samples were collected to determine the baseline serum levels of selenium, copper, zinc, iron, malondialdehyde and glutathion peroxidase. Anesthesia was induced using 2−2.5 mg kg^{-1} propofol, 1 mg kg^{-1} lidocaine and 0.6 mg kg^{-1} rocuronium. In the maintenance of anesthesia, under carrier gas of 50:50% O_2:N_2O 4 L min^{-1}, 1 MAC sevoflurane was administered to Group S and 1 MAC desflurane to Group D; and under carrier gas of 50:50% O_2:air 4 L min^{-1} 6 mg kg h^{-1} propofol and 1 μg kg h^{-1} fentanyl infusion were administered to Group P. At postoperative blood specimens were collected again.

Results: It was observed that only in Group S and P, levels of MDA decreased at postoperative 48th hour; levels of glutathion peroxidase increased in comparison to the baseline values. Selenium levels decreased in Group S and Group P, zinc levels decreased in Group P, and iron levels decreased in all three groups, and copper levels did not change in any groups in the postoperative period.

Conclusion: According to the markers of malondialdehyde and glutathion peroxidase, it was concluded that maintenance of general anesthesia using propofol and sevoflurane activated

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the antioxidant system against oxidative stress and using desflurane had no effects on oxidative stress and antioxidant system.

Efeitos da manutenção de várias anestesias sobre os níveis séricos de selênio, cobre, zinco e ferro e a capacidade antioxidante

Resumo

Justificativa e objetivos: Investigar os efeitos da manutenção de sevoflurano, desflurano e propofol sobre nos níveis séricos de selênio, cobre, zinco, ferro e malondialdeído, as mensurações de glutationa peroxidase e a capacidade antioxidante.

Métodos: Foram alocados em três grupos 60 pacientes agendados para cirurgia unilateral de membros inferiores, feita com torniquete sob anestesia geral. Amostras de sangue foram coletadas para determinar os níveis séricos basais de selênio, cobre, zinco, ferro, malondialdeído e glutationa peroxidase. A anestesia foi induzida com 2-2,5 mg kg^{-1} de propofol, 1 mg kg^{-1} de lidocaína e 0,6 mg kg^{-1} de rocurônio. Na manutenção da anestesia, sob gás de transporte de 50% O_2 e 50% N_2O (4 L min^{-1}), sevoflurano a 1 CAM foi administrado ao Grupo S e desflurano a 1 CAM ao Grupo D e, sob gás de transporte em mistura de 50% O_2 e 50% ar (4 L min^{-1}), 6 mg kg h^{-1} de propofol e 1 mg kg h^{-1} de fentanil foram administrados ao Grupo P. No pós-operatório, amostras de sangue foram novamente coletadas.

Resultados: Apenas nos grupos S e P os níveis de MDA diminuíram em 48 horas de pós-operatório; os níveis de glutationa peroxidase aumentaram em comparação com os valores basais. Os níveis de selênio diminuíram no Grupo S e no Grupo P, os níveis de zinco diminuíram no Grupo P, os níveis de ferro diminuíram em todos os grupos e não houve alteração nos níveis de cobre em nenhum grupo no período pós-operatório.

Conclusão: De acordo com os marcadores de malondialdeído e glutationa peroxidase, concluímos que a manutenção da anestesia geral com propofol e sevoflurano ativou o sistema antioxidante contra o estresse oxidativo e o uso de desflurano não teve efeitos sobre o estresse oxidativo e o sistema antioxidante.

Introduction

The purpose in general anesthesia practices is to decrease the potentially harmful conditions for the organism to the lowest level as well as conducting the anesthesia effectively. During general anesthesia, stress due to anesthesia and surgery and immunological defense mechanisms can be disrupted, and macrophages cause releasing of free oxygen to the environment by inducing inflammatory reaction. These radicals lead formation of toxic metabolites such as malonyl dialdehyde (MDA) by causing cellular damage with lipid preoxidation.[1,2]

MDA is used as an indirect indicator of oxidative damage that its level can be detected in the systemic circulation, and as a marker of ischemia–reperfusion damage.[3]

Antioxidant enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) play role as the defense mechanism in the body against tissue damage caused by reactive oxygen substrates (ROCs).[4] Activities of these enzymes are dependent on the synthesis and degradation rates of free radicals, nutrition, and condition of trace elements. Trace elements play cofactor-key role in cleaning of free oxygen radicals in antioxidant systems.[5,6]

Tourniquet is used to decrease bleeding in extremity surgery, and presence of ischemia reperfusion damage caused by free oxygen radicals depending on tourniquet application was shown in previous studies.[7] Use of immunosuppressants, corticosteroids, anesthetics, various anesthetic methods and antioxidants for the purpose of decreasing free radicals in the prevention of this damage was studied.[3,8–10]

It was shown in the studies that effects of anesthetic agents on oxidative stress and antioxidant capacity vary.[1,11,12] Volatile anesthetics were shown to induce oxidative stress and inflammatory response with causing relasing of free radicals such as inflammatory mediators and superoxide anions, with decreasing antioxidant defense mechanisms, and with inducing gene expression of proinflammatory cytokines, as well as it was reported that some anesthetics could also have antioxidant effects.[13–19] Besides this, it was stated that anesthetic agents could trigger oxidative stress, and could cause decrease in serum trace elements.[20,21]

In the present study, we planned to research effects of three different general maintenance of anesthesia (sevoflurane, desflurane and propofol) on trace elements, oxidative stress and antioxidant capacity with measuring serum levels of Se, Cu, Zn, Fe, MDA and GPx in the patients who were planned to undergo extremity surgery with applying tourniquet.

Materials and methods

This study was conducted prospectively with approval of the Bulent Ecevit University Ethics Committee (08.03.2011, Meeting decision no: 2011/02) and after receiving written informed consent forms from the patients.

A total of 60 patients over 18 years old and between 60 and 100 kg in weight who were American Society of Anesthesiologists Status (ASA) I–III and who were planned lower extremity surgery with applying a unilateral tourniquet in elective conditions and under general anesthesia were included in the study. The exclusion criteria were the presence of any cardiovascular, respiratory and cerebrovascular diseases, severe liver or kidney failure (creatinin clearence < 60 mL min^{-1}), diabetes mellitus, pregnancy, obesity (BMI > 30 kg m^2), autoimmune disease, history of treatment with immunosuppressants, history of Se, Zn, Cu, Fe and antioxidant therapy within the last three months, history of allergy to the drugs that would be used, and cases with a tourniquet period shorter than 60 min or longer than 150 min.

The cases were randomly divided into three equal groups [Group S (sevoflurane), Group D (desflurane), Group P (propofol)].

Premedication of midazolam 0.07 mg kg^{-1} was administered to all patients 30 min before the operation. Standard anesthesia monitorization [electrocardiogram (ECG), peripheral oxygen saturation (SpO$_2$) and noninvasive arterial blood pressure] was performed for the patients taken into the operation room, and baseline values were recorded. A vascular access was established through a wide cubital vein using a 16 G angiocath. Blood samples were taken for detection of baseline (T1) serum levels of Se, Cu, Zn, Fe, MDA and GPx. A vascular access was established in the other arm for liquid infusions using a 20 G angiocath. Saline infusion of 8–10 mg kg h^{-1} was started.

All the patients were administered preoxygenation with 10 L min^{-1} of 100% oxygen for 1 min. Anesthesia induction was provided using 2–2.5 mg kg^{-1} of propofol and 1 mg kg^{-1} of lidocaine. Intubation was performed 2 min after administration of 0.6 mg kg^{-1} of rocuronium as the muscle relaxant.

Maintenance of anesthesia was provided under 4 L min^{-1} carrier gas as 50:50% O$_2$:N$_2$O using 1 MAC sevoflurane in Group S, under 4 L min^{-1} carrier gas as 50:50% O$_2$:N$_2$O using 1 MAC desflurane in Group D, and administering 4 L min^{-1} fresh gas as 50:50% O$_2$:air using 6 mg kg h^{-1} propofol and i.v. infusion of 1 μg kg h^{-1} fentanyl in Group P. In all three groups, ventilation tidal volume was provided as 6–8 mL kg^{-1}, I:E rate was 1:2, and respiration rate was provided to achieve normocapnia as setting the Et CO$_2$ level to 35–40 mmHg.

Following the intubation, the extremity that would be operated was wrapped using Esmarch bandage after it was elevated, and tourniquet was applied at a pressure of 300 mmHg. It was planned to administer 50 μg i.v. fentanyl in cases of increase of 20% or more in the baseline values of intraoperative arterial blood pressure or heart rate.

Patients' demographic data, operative and tourniquet time, bleeding, quantities of the blood given, ASA levels, smoking and alcohol abuse (recorded as present/none), types of operations (recorded as 1 – foot fracture, 2 – tibia fracture, 3 – knee meniscopathy, 4 – ankle fracture, 5 – knee prosthesis), occupational groups (recorded as 1 – miners, 2 – self-employed, 3 – officer, 4 – smith, 5 – welder, 6 – unemployed), intraoperative additional drug use (recorded as 1 – none, 2 – pheniramine maleate + dexamethasone, 3 – methylprednisolone + ranitidine, 4 – glyceryl trinitrate), postoperative additional problems (recorded as 1 – present, 2 – none, 3 – bronchospasm, 4 – nausea, 5 – vomiting, 6 – itch) were saved. When the last skin suture was started before the operation ended, the patients were ventilated using 100% O$_2$ after anesthetics were discontinued. Muscle relaxant effect was antagonized using 0.05 mg kg^{-1} neostigmine and 0.01 mg kg^{-1} atropine intravenously.

All the patients were administered 1 mg kg^{-1} i.v. tramadol for postoperative pain control 15 min before the operation ended. Postoperative analgesia was maintained using tramadol as 10 mg bolus and 10 min lock with patient-controlled analgesia (PCA) method. Amount of tramadol consumed was recorded.

Blood samples were taken again for detection of serum levels of Se, Cu, Zn, Fe, MDA, and GPx in the postoperative 0th (T2), 24th (T3), and 48th (T4) hours. The blood samples were centrifuged at 5000 rpm for 5 min in the biochemistry laboratory immediately, and the serum extracted were stored at −40 °C.

MDA measurement

Serum MDA levels were tested using commercial kits (Immundiagnostik, Bensheim, Germany) by high performance liquid chromatography (HPLC) method with an HPLC device (Agilent 1200, Munich, Germany). Working principle of the test is based on conversion of MDA to a fluorescent product as a result of a sample preparation process performed using a derivation reactive. Fluorometric measurement was done in 515 nm excitation and 553 nm emission after separation of 20 μL reaction mix containing MDA converted to a fluorescent product using reverse phase C 18 column at 30 °C. Detection limit of the method was 0.15 μmol L^{-1}, and its linearity was 100 μmol L^{-1}.

GPx measurement

Serum GPx activity was measured with Paglia and Valentine method. H$_2$O$_2$ was used as substrate in the measurement of enzyme activity, and NADPH oxidation was detected spectrophotometrically at 340 nm. The results were expressed as U L^{-1}.

Measurements of trace elements

Copper and zinc

Serum Cu and Zn levels were measured using commercial kits (FAR-SRL, Verona, Italy) in UV-1601 spectrophotometer device (Shimadzu, Tokyo, Japan) with colorimetric method.
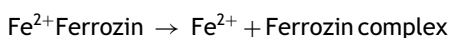
Selenium

The study was conducted using Perkin Elmer branded Atomic Absorption Spectrometer (AAS), and hydride system (FIAS) was used as follows: 1 unit serum + 6 unit acid solution (perchloric/nitric acid solution, 5/1) was hydrolysed at 120 °C for 1 h. A total of 3 mL 50% HCl was added, and was hydrolysed at 120 °C for 1 h again. Then 3 mL water was added and the last read was done. Five-point calibration was performed using Inorganic Ventures branded stock. Two levels were used as controls such as Serenom Trace Elements Serum L-1 (selenium level 100–114 μg L^{-1}) and Serenom Trace Elements Serum L-1 (selenium level 153–173 μg L^{-1}). The reference range was 46–143 μg L^{-1} for serum selenium level in the laboratory that the measurement was performed.

Iron

Iron measurement was carried out using the Ferrozine method. According to this method, iron was released from transferrin under acidic conditions, was reduced to ferrous form, and was coupled with a chromogen for the colorimetric measurement. In this procedure, iron was measured directly without any steps of protein denaturation or any interactions with an endogenous copper.

Ferric iron was separated from the carrier protein transferrin in acidic condition, and was reduced simultaneously to ferrous form. Then iron formed a complex with ferrozine, a sensitive iron indicator, and formed a colored chromophore that exhibits absorbance at 571/658 nm.

Reaction equation

$$\text{Transferrin(Fe}^{3+}) \rightarrow \text{Apotransferrin} + \text{Fe}^{3+}$$

$$\text{Fe}^{3+} + \text{AscorbicAcid} \rightarrow \text{Fe}^{2+}$$

$$\text{Fe}^{2+}\text{Ferrozin} \rightarrow \text{Fe}^{2+} + \text{Ferrozin complex}$$

Reference values

Male: 65–175 μg/dL (11.6–31.3 μmol/L).
Female: 50–170 μg/dL (9.0–30.4 μmol/L).

Statistical analysis

Survey data collected during the research were transferred to the software ''SPSS for Windows 16.0'', and were analyzed. Average values were expressed as mean ± standard deviation (SD). The chi-square test was used in the comparison of distribution of qualitative data such as gender, ASA, occupation, mining history, types of operation, smoking, alcohol consumption, intraoperative additional drug use, postoperative additional problems according to the groups.

Kruskal–Wallis ANOVA and Mann–Whitney U tests were used in comparisons between the groups in terms of continuous variables such as durations of operation and tourniquet, intraoperative bleeding, blood amounts given, serum levels of Se, Cu, Zn, Fe, MDA, and GPx, and amounts of tramadol consumption. Friedman and Wilcoxon tests were used in comparison of these variables with preoperative baseline values within the groups.

Analysis results were evaluated within confidence interval of 95%, and $p < 0.05$ values were accepted as statistically significant.

Results

No significant differences were found in terms of demographic data and ASA risk classification of the study groups (Table 1).

No significant differences were found between the groups in terms of types of operation and occupation ($p > 0.05$), however, significant difference was found in terms of history of alcohol consumption ($p < 0.05$) (Table 2).

No significant difference was found between the groups in terms of tramadol consumption amounts either intraoperative or postoperative periods ($p > 0.05$) (Fig. 1). Tramadol consumption amounts.

Data concerning the durations of operations and tourniquet application, intraoperative bleeding amounts, blood amounts given (as units), intraoperative additional drug use, and postoperative additional problems are shown on Table 3. Tourniquet duration and intraoperative bleeding amounts of Group D were found to be significantly lower than Group S ($p < 0.05$). Durations of operations and tourniquet applications and intraoperative bleeding amounts were found to be significantly lower in Group D in comparison to Group P ($p < 0.05$). Intraoperative blood transfusion was performed just in Group S. No significant differences were found between the groups in terms o the other variables ($p > 0.05$).

No significant difference was detected between the groups in terms of Se levels ($p > 0.05$) (Fig. 2). A significant difference was found within the groups in terms of temporal changes in Se levels ($p < 0.05$). T2 and T4 values in Group S, and T3 and T4 values in Group P were found to be

Table 1 Demographical data and ASA risk classification of the study groups.
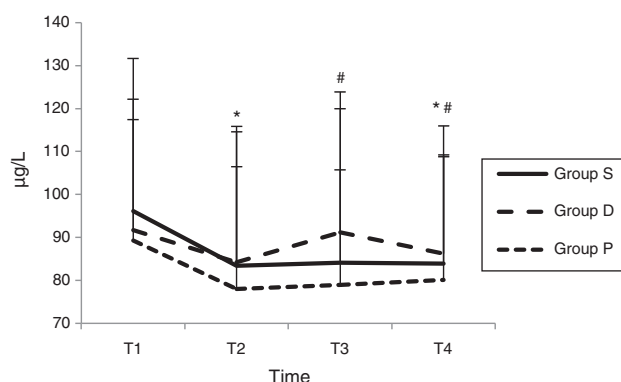
	Group S ($n = 20$)	Group D ($n = 20$)	Group P ($n = 20$)	p
Gender (M/F)	16/4	13/7	11/9	0.241
Age (year)	41.8 ± 12.2	39.4 ± 14.2	41.0 ± 17.7	0.845
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.753
Weight (kg)	71.9 ± 11.1	77.1 ± 12.1	75.7 ± 11.0	0.180
BMI	24.7 ± 2.9	26.1 ± 3.3	25.6 ± 3.6	0.236
ASA (I/II/III)	6/12/2	5/11/4	5/14/1	0.644

ASA, American Society of Anesthesiologist.

Table 2 Types of operation, occupation, and history of alcohol consumption and smoking according to the groups.

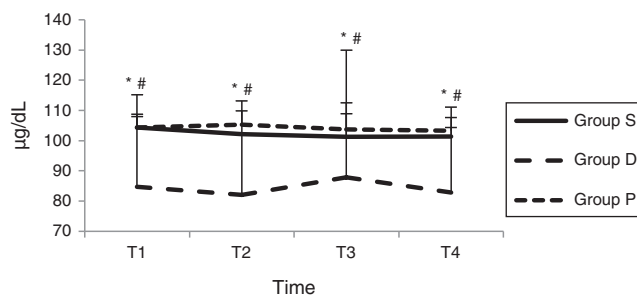|	Group S (n = 20)	Group D (n = 20)	Group P (n = 20)	p
Occupation[a] (1/2/3/4/5/6)	3/9/3/1/2/2	4/5/3/1/0/7	1/9/3/0/0/7	0.337
Operation type[b] (1/2/3/4/5)	4/9/5/2/0	0/6/1/3/0/1	3/6/6/2/3	0.063
Smoking (+/−)	12/8	8/12	9/11	0.420
Alcohol (+/−)	1/19	0/20	5/15	0.020

+, yes; −, no.
[a] Occupational groups recorded as 1 – miners, 2 – self-employed, 3 – officer, 4 – smith, 5 – welder, 6 – unemployed.
[b] Types of operations recorded as 1 – foot fracture, 2 – tibia fracture, 3 – knee meniscopathy, 4 – ankle fracture, 5 – knee prosthesis.
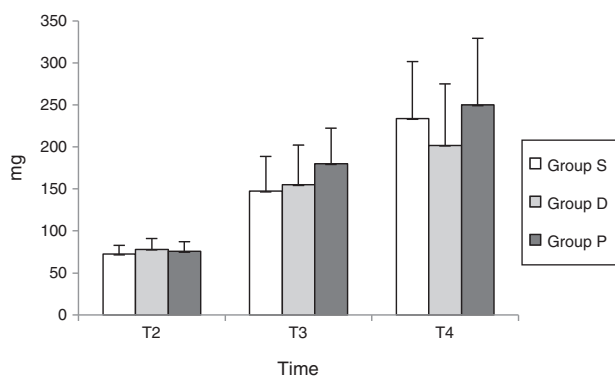
Figure 1 Tramadol consumption (mg). T2, postoperative 0th; T3, postoperative 24th; and T4 postoperative 48th hours

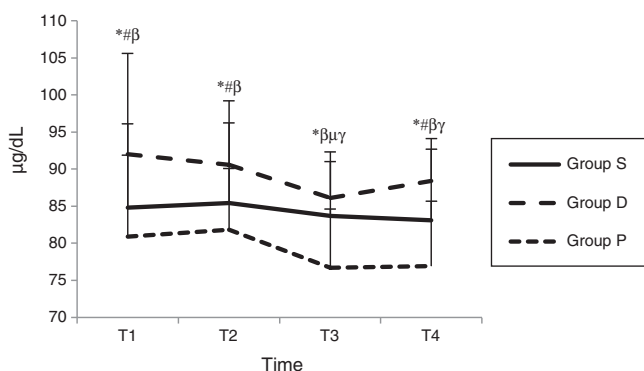significantly lower than the baseline values measured at T1 ($p < 0.05$).

Cu levels were found to be significantly different between the groups in each measurement time ($p < 0.05$). Serum Cu levels were lower in Group D in comparison to the other groups in each measurement. No difference was found within the groups in terms of temporal changes in Cu levels in comparison to the baseline values ($p > 0.05$) (Fig. 3).

Significant differences were found between the groups in terms of Zn levels in each measurement time ($p > 0.05$). Serum Zn levels were found to be significantly higher in Group D in comparison to Group S at T1, T2, and T4 times, and in comparison to Group P at T1, T2, T3, and T4 times ($p < 0.05$). When the temporal changes in Zn levels were assessed, T3 value in Group D, and T3 and T4 values in Group P were found to significantly lower in comparison to the baseline values measured at T1 time ($p < 0.05$) (Fig. 4).

Figure 2 Serum Se levels (μg/L). *$p < 0.05$ T2 and T4 values compared with T1 basal values in Group S; #$p < 0.05$ T3 and T4 values compared with T1 basal values in Group P; T1, basal values; T2, postoperative 0th; T3, postoperative 24th; and T4, postoperative 48th hours.

Figure 3 Serum Cu levels (μg/dL). *$p < 0.05$ comparison across groups; #$p < 0.05$ Group S and Group P compared with Group D; T1, basal values; T2, postoperative 0th; T3, postoperative 24th; and T4, postoperative 48th hours.

Table 3 Distribution of durations of operations and tourniquet applications and intraoperative bleeding, blood amounts given, intraoperative additional drug use, postoperative additional problems (mean ± SD).

	Group S (n = 20)	Group D (n = 20)	Group P (n = 20)	p
Operation duration (min)	137.7 ± 67.3	102.7 ± 34.6	160.5 ± 62.0[a]	0.005
Tourniquet duration (min)	88.4 ± 21.6[a]	77.2 ± 22.3	101.0 ± 21.7[a]	0.004
Intraoperative bleeding (mL)	163.5 ± 245.2[a]	52.5 ± 51.5	168.0 ± 107.6[a]	0.000
Blood amounts given (unit)	0.2 ± 0.5	0.0 ± 0.0	0.0 ± 0.0	0.045
Additional drug use[b] (1/2/3/4)	19/1/0/0	15/0/4/1	14/2/2/2	0.181
Postoperative additional problem (no/bronchospasm)	20/0	18/2	20/0	0.126

[a] $p < 0.05$: when compared with Group D.
[b] Additional drug use recorded as 1 – none, 2 – pheniramine maleate + dexamethasone, 3 – methylprednisolone + ranitidine, 4 – glyceryl trinitrate.
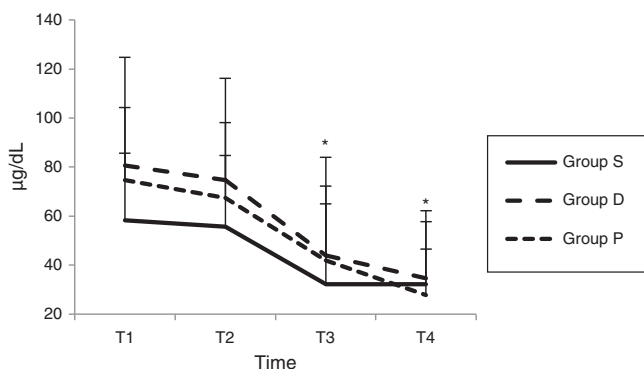
Figure 4   Serum Zn levels (μg/dL). *$p < 0.05$ comparison across groups; #$p < 0.05$ Group S compared with Group D; $\beta$$p < 0.05$ Group P compared with Group D; $\mu$$p < 0.05$ T3 values compared with T1 basal values in Group D; $\gamma$$p < 0.05$ T3 and T4 values compared with T1 basal values in Group P; T1, basal values; T2, postoperative 0th; T3, postoperative 24th; and T4, postoperative 48th hours.
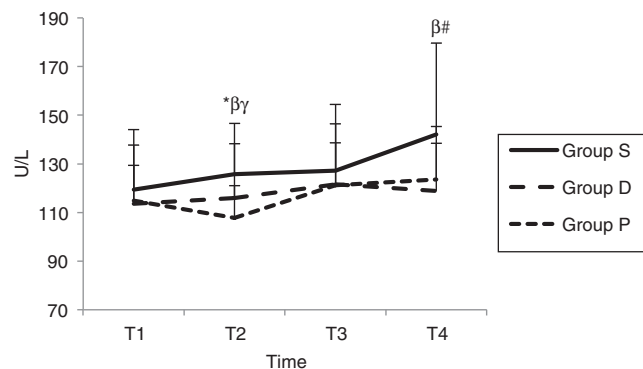
No significant difference was found between the groups in terms of Fe levels ($p > 0.05$). When the temporal changes in Fe levels within the groups were assessed, T3 and T4 Fe levels were found to be significantly lower than the baseline values measured at T1 time ($p < 0.05$) (Fig. 5).

A significant difference was observed between the groups in the value measured at T2 time in terms of GPx levels ($p < 0.05$). Serum GPx level measured at T2 time was found to be significantly higher in Group S in comparison to Group P ($p < 0.05$). When the temporal changes in GPx levels were assessed within the groups, T4 values both in Group S and Group P were found to be significantly higher than the baseline values measured at T1 time ($p < 0.05$). No significant differences were found within Group D in terms of temporal changes at any times (Fig. 6).
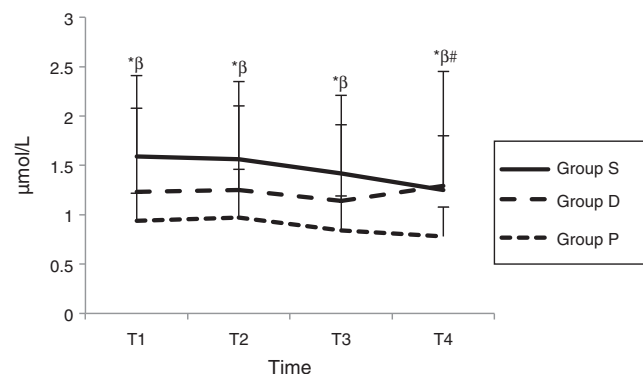
Significant differences were found at each measurement time between the groups in terms of MDA values ($p < 0.05$). MDA values were higher in Group S in comparison to Group D at T1, and in comparison to Group P at T1, T2, T3, and T4 times ($p < 0.05$). When the temporal changes in MDA levels were assessed within the groups, T4 values were found to be significantly lower in Group S and Group P at T4 in

Figure 5   Serum Fe levels (μg/dL). *$p < 0.05$ all groups T3 and T4 levels compared within itself with T1 basal values; T1, basal values; T2, postoperative 0th; T3, postoperative 24th; and T4, postoperative 48th hours.

Figure 6   Serum GPx Levels (U/L). *$p < 0.05$ comparison across groups; $\gamma$$p < 0.05$ Group P compared with Group S; #$p < 0.05$ T4 values compared with T1 basal values in Group S; $\beta$$p < 0.05$ T2 and T4 values compared with T1 basal values in Group P; T1, basal values; T2, postoperative 0th; T3, postoperative 24th; and T4, postoperative 48th hours.

Figure 7   Serum MDA levels (μmol/L). *$p < 0.05$ comparison across groups; #$p < 0.05$ T4 values compared with T1 basal values in Group S and Group P; $\beta$$p < 0.05$ Group P compared with Group S; T1, basal values; T2, postoperative 0th; T3, postoperative 24th; and T4, postoperative 48th hours.

comparison to the baseline values measured at T1 ($p < 0.05$) (Fig. 7).

Discussion

In the present study conducted on the cases wo underwent extremity surgery using tourniquet under general anesthesia, it was observed that both sevoflurane and propofol maintenance decreased Se and MDA levels, and increased GPx values, sevoflurane did not change Zn levels but propofol decreased Zn levels, and that implementation of desflurane did not cause changes in Zn, Se, MDA, and GPx levels. Besides this, all these three different general anesthesia maintenance significantly increased serum Fe levels in comparison to the baseline values, and did not change Cu levels.

It was reported that anesthetic agents could antioxidant activity in ischemia reperfusion damage due to tourniquet via preventing of formation of highly reactive oxygen radicals as well as they inhibited leukocyte functions.[22–24]

Allaouchiche et al.,[11] compared the activities of anesthesia of propofol (8 mg kg h^{-1}), desflurane (10%), and

sevoflurane (2.5%) in pigs for determination of effect of general anesthesia on oxidative condition. In their study that they evaluated plasma and alveolar concentrations of MDA, SOD and GPx during general anesthesia for 120 min, they showed that propofol caused increase in GPx levels either in bronchoalveolar lavage (BAL) fluid or in circulation, and decrease in MDA levels. In contrast, they found that desflurane caused increase in MDA levels both in BAL fluid and in circulation, and decrease in GPx values. They reported no significant changes in both GPx and MDA levels either in BAL fluid or in circulation in the group that sevoflurane was administered. As a result, they concluded that desflurane had a potential effect of increasing the oxidative stress, propofol had positive effects on antioxidant system via decreasing lipid peroxidation, and that sevoflurane had no effects on oxidative stress and antioxidant system. In our study, general anesthesia with propofol caused increase in GPx levels, and decrease in MDA. Sevoflurane concentration used in the study of Allaouchiche et al.,[11] was 2.5%, and it was 2% in our study. Besides this, it is well known that N_2O itself could increase oxidative stress via causing formation of reactive oxygen species.[25] In our study, we considered that the increase in GPx levels in the sevoflurane group in comparison to the baseline values might have been caused by the difference in concentration of sevoflurane used, and by use of N_2O as the carrier gas.

In the previous reports, similar to the present study, it was reported that sevoflurane prevented myocardial dysfunction and necrosis in post-myocardial ischemia reperfusion phase; it effected oxidative stress and antioxidant mechanisms positively by causing less lipid peroxidation in laparoscopic cholecystectomy; it protected the heart against ATP depletion induced by ischemia, calcium currents, and oxidative stress via protein kinase activation, opening of mitochondrial K+ATPase channels, and formation of reactive oxygen particles; it decreased adhesion of postischemic polymorphonuclear neutrophils; and that it had more antioxidant activity in comparison to spinal anesthesia.[1,26–30]

In the studies in which administrations of sevoflurane and desflurane in laparoscopic surgery were compared, it was shown that desflurane increased oxidative stress more, and that it changed antioxidant mechanisms negatively.[1,12] Besides this, it was stated that this effect increased more when desflurane and nitrogen mix was used.[12]

It was shown that propofol had a supportive effect to antioxidant capacity, and that it inhibited production of lipid peroxidase in the previous studies.[31–33] Antioxidant effect of propofol was attributed to its chemical similarity to the other known antioxidants such as butylhydroxytoluene and alpha-tocopherol.[32,34,35] These antioxidants bind membrane phospholipids, and capture free radicals, and so they show antioxidant properties by inhibiting the transmission chain with membrane fatty acid molecules.[36]

It was reported that in the cases with knee artroplasty that ischemia reperfusion damage developed due to tourniquet, propofol showed antioxidant effect by decreasing MDA levels below the baseline values after opening the tourniquet.[37]

Arnaoutoglou et al.,[38] found that MDA levels decreased in comparison to the baseline values in the propofol group, and increased in a small amount in the sevoflurane group

30 min after the opening of the tourniquet in their study in which they researched the effects of the group they administered 6–10 mg kg^{-1} propofol maintenance after induction of 3 μg kg^{-1} fentanyl + 2–2.5 μg kg^{-1} propofol, and of the group that they administered sevoflurane in 1.5–2% concentration under 66:33% $N_2O:O_2$ carrier gas maintenance after induction of 3 μg kg^{-1} fentanyl + 5 mg kg^{-1} thiopental in ischemia–reperfusion damage due to tourniquet in knee surgery on MDA levels. MDA, in fact, is a lipid peroxidation indicator that may increase in early periods. Our MDA measurements were performed earlier in comparison to the study of Arnoutoglou et al., and $N_2O:O_2$ concentration we used was also less. We administered propofol to our all groups for induction. In contrast to the study of Arnaoutoglu et al., we considered that antioxidant activity of sevoflurane might be caused by these factors.

It is considered that desflurane may cause less oxidative stress, and less antioxidant activity depending on its less metabolism. In the study of Türkan et al.,[39] that they investigated oxidative conditions of sevoflurane and desflurane in erythrocytes, they showed that desflurane had no oxidant or antioxidant activities though several studies reported that desflurane had local and systemic antioxidant activity.[1,12,11,40,41] It was stated that oxidative stress developed by desflurane anesthesia in pig lungs could be related to excessive increase in proinflammatory cytokines in macrophages.[11] Ceylan et al.,[42] found that desflurane caused lipid peroxidation by decreasing vitamin E levels in the patients underwent surgery under desflurane anesthesia.

It was shown that free radicals formed during ethanol metabolism in alcohol consumption caused increase in oxidative stress, and that they had negative effects on antioxidant capacity.[43,44] Besides this, it is known that cell damage and oxidative stress due to ischemia–reperfusion increase depending on the severity and duration of ischemia.[45]

Wardle et al.,[46] reported that oxidative damage increased following blood transfusion in premature infants. It was stated that the association between blood transfusion and MDA levels might be due to oxidative effect of excess free Fe formed by destruction of erythrocytes.[47] Free iron causes tissue damage via formation of highly reactive hydroxyl radicals from H_2O_2 and superoxides with Fenton and Haber–Weiss reactions.[48] In our study blood transfusion was not performed in two groups other than the sevoflurane group.

In the present study, when analysing the factors of the lack of oxidative stress in the desflurane group, we considered that it might have been caused by lack of alcohol consumption, shorter duration of tourniquet application in comparison to the other groups, and lack of use of blood products in the desflurane group.

In the previous studies, it was shown that plasma MDA levels increased in smokers as an indicator of lipid peroxidation.[49] In the present study, we believe that smoking had no influence on the results due to lack of difference between the groups in terms of smoking.

There are extracellular proteins such as GPx, SOD, and CAT enzymes, albumin, transferrin, and lactoferrin amongst antioxidant enzyme systems. Activity of these enzymes depends on synthesis and degradation rates of free radicals,

nutrition, and taking of trace elements (Se, Mn, Zn, Cu, Fe). Amongst the antioxidant enzymes, Cu, Zn, and Mn are found in the structure of SOD, and Se ion is found in GPx.[5,6]

Selenium has numerous biological functions, and the most important one of these is antioxidant activity. This activity depends on the presence of selenocystein in activity in thioredoxins reductases and GPxs. Therefore, activities of these enzymes decrease in cases that serum Se levels are low.[50,51] In their study that they investigated genotoxic effects of repeating sevoflurane anesthesia in rabbits using Comet test, Kaymak et al.,[52] reported that selenium support administered into periton had protective role against DNA damage caused due to anesthesia.

It was reported that changes in the levels of trace elements caused increase in negative effects of free oxygen radicals on the integrity of the cell by decreasing the efficiency of antioxidant defense mechanism. Trace elements, particularly Zn, Cu, and Fe, have significant effects on lipid peroxidation.[53] Salonen et al.,[54] showed that myocardial infarction risk was four times more in the humans with high plasma Cu levels in comparison to the normal population as a result of negative effects of lipid peroxidation on the vessel walls.

Zn, cofactor of SOD enzyme, plays an important role in capturing of free oxygen radicals. In SOD enzyme, Zn causes the enzyme to keep the stability, and Cu is responsible for the activity of the enzyme.[55-57] Zn levels decreased after surgery may reduce the activity of the enzyme, and may cause increase in serum Cu levels depending on this.[58,59]

In the individuals with cancer, it was stated that serum Cu/Zn rate did not change in the early stages, but this rate increased significantly in the advanced stages.[60] It was reported that an increased Cu/Zn rate either in the tissue or in serum might indicate an impaired antioxidant defense.[57] In the present study, when the measurements of 48th hour were compared to the baseline values, Cu levels have not changed, and Zn levels decreased in the propofol group, and no differences were observed in the sevoflurane and the desflurane groups in terms of Cu and Zn.

The most important feature of iron is its capability to be found in two-oxidation condition as ferric and ferrous forms. Iron in ferric form is non-functional. Most of the iron (75%) is found bound to hem proteins such as hemoglobin and myoglobin. The rest is found in storage proteins such as ferritin and hemosiderin, and in critical enzyme systems such as CAT involved in cytochrome and antioxidant systems.[61] It was shown that increased oxidative stress might play role in the pathogenesis of iron deficiency anemia that better responses might have been provided by administration of antioxidant vitamins together with iron replacement therapy in the patients with iron deficiency anemia, and so that earlier improvement of the symptoms related to iron deficiency anemia could be achieved.[62] In our study, iron levels decreased in all three groups in the postoperative period ($p < 0.05$).

Türkan et al.,[20] found that antioxidant enzyme activity of erythrocyte (SOD, GPx) and trace element levels decreased in the patients who were administered halothane, enflurane and isoflurane anesthesia. In another study of Türkan et al.,[21] levels of SOD and GPx antioxidant enzymes and cofactors of these, Se, Cu, and Zn, were shown to be lower in the individuals exposed to anesthetic gases chronically in the operation rooms with passive waste systems in comparison to the staff of the other departments of the hospital who were not exposed to these gases. As a result of the mentioned study, it was reported that exposure to anesthetic gases chronically had influence on antioxidant enzyme system.

As a result of evaluation of the indicators such as MDA and GPx, we concluded that general anesthesia maintenance using propofol activated antioxidant system against oxidative stress and decreased Se and Zn levels due to use of antioxidant system; general anesthesia maintenance using sevoflurane activated antioxidant system against oxidative stress and decreased Se levels due to use of antioxidant system; general anesthesia maintenance using desflurane had no impacts on oxidative stress and antioxidant system and so did not cause changes in trace element levels, however that each three methods decreased serum iron levels.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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