

Effects on the Lipid Peroxidation and the Antioxidant Defense Systems of the Use of Isoflurane or Sevoflurane in Calves Undergoing Surgery

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ABSTRACT

Background: Incoming anaesthesia created by the use of many drugs with different physicochemical properties is a source of stress and trauma for the body. This event increases the oxidative response and changes the balance between oxidant/antioxidant capacity in the organism in favor of oxidant capacity. This situation is defined as oxidative stress. For these reasons, studies are conducted to determine the effects of general anaesthetic agents on oxidant and antioxidant systems in the organism. In this study, it was aimed to determine the effects of isoflurane and sevoflurane used for general anaesthesia in humans and animals on lipid peroxidation and antioxidant defense system in calves.

Materials, Methods & Results: The study included 14 calves of different breeds, ages, sexes, and weighing, average 2 weeks old. The cases randomly were divided into 2 groups, the isoflurane group (group I), and the sevoflurane group (group II), and each group included 7 animals. Before general anaesthesia, 0.04 mg/kg atropine was administered intramuscularly to all animals for premedication. At 15 min after atropine administration, isoflurane was administered at an inspiratory concentration of 3-5% in group I, and sevoflurane was administered at an inspiratory concentration of 5-7% in group II, via a face mask for 15 min for the induction of anaesthesia. Endotracheal intubation was performed in all cases at the 15 min of the induction period following the onset of general anaesthesia symptoms. After the induction, anaesthesia was continued at an inspiratory concentration of 1.5-3% in the isoflurane group and inspiratory concentration of 2.5-4% in the sevoflurane group. Blood samples were taken just before anaesthesia, just before skin incision, at the end of anaesthesia and surgery, and at the 24 h postoperatively. The malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and glutathione (GSH) levels were measured spectrophotometrically in samples. In group I, MDA and antioxidant parameters SOD, CAT, GSH-Px, GSH did not observe a significant change in their concentrations through the study ($P > 0.05$). In group II, MDA value decreased significantly before incision ($P < 0.05$), at the end of anaesthesia and surgery compared to the pre-anaesthesia level ($P < 0.001$), and then although increased significantly at 24 h postoperatively, the value was still lower than the pre-anaesthesia level ($P < 0.05$). It was determined that SOD activity increased significantly after sevoflurane compared to pre-anaesthesia ($P < 0.05$) however, the increases in SOD activity detected during sevoflurane were not statistically significant ($P > 0.05$). During the study, a statistically insignificant increase was observed in the concentrations of CAT, GSH-Px, GSH compared to pre-anaesthesia ($P > 0.05$). Pre-anaesthesia values of all measured biochemical parameters did not differ significantly between groups ($P > 0.05$). Before skin incision, at the end of anaesthesia and surgery, and at the 24 h postoperatively MDA was lower ($P < 0.05$) and SOD activity was higher ($P < 0.05$) than in group I in group II. There was no statistically significant difference between the two groups in terms of CAT, GSH-Px, GSH levels between the other measurement times ($P > 0.05$).

Discussion: An important advantage of sevoflurane compared to currently available anaesthetics is that it provides rapid induction due to its low solubility in blood and tissues, and rapid recovery due to its low solubility in fat. This feature is proof that the side effects of sevoflurane anaesthesia are minimal. The findings of this study show that sevoflurane exposure decreases lipid peroxidation and enhances antioxidant defense. The potential effect of sevoflurane on oxidative stress may lead to its preferred clinical use of sevoflurane compared to isoflurane.

Keywords: isoflurane, sevoflurane, lipid peroxidation, antioxidants, calve.

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INTRODUCTION

The purpose of an ideal general anaesthesia application is to provide the conditions that will least harm the physiology and metabolism of the organism. Since the anaesthetic agents used today do not fully meet these requirements, new agents are developed and the effects of these agents on the organism are investigated [3,34]. For this purpose, isoflurane and sevoflurane are among the most researched anaesthetic agents [15,39,40]. Incoming anaesthesia created by the use of many drugs with different physicochemical properties is a source of stress and trauma for the body [10,17,18,20,41]. This event increases the oxidative response and changes the balance between oxidant / antioxidant capacity in the organism in favor of oxidant capacity. This situation is defined as oxidative stress [11,37,38]. Oxidative stress causes damage to many biological materials such as proteins, lipids, DNA and nucleotides, and coenzymes in the organism. There is information that this damage promotes aging and also causes many diseases such as cardiovascular diseases, various types of cancer, cataracts, weakened immune system, nervous system degenerative diseases [12,19,37,38]. For these reasons, studies are carried out to determine of the effects on the oxidant and antioxidant system in the organism of anaesthetic agents used to create an ideal general anaesthesia.

In this study it was aimed to determine the effects of isoflurane and sevoflurane inhalation anaesthesia used for general anaesthesia in humans and animals on lipid peroxidation and antioxidant defense system in calves.

MATERIALS AND METHODS

Animals

The study included 14 calves of different breeds, ages, sexes, and, weighing, average 2 weeks old, that was brought to the Surgical Clinics of Kafkas University Faculty of Veterinary Medicine due to diseases requiring surgical intervention. The cases randomly were divided into 2 groups, the isoflurane group (group I), and the sevoflurane group (group II) with 7 animals in each group.

Anaesthesia protocol

Atropine (Atrol-R®)¹ 0.04 mg/kg was administered intramuscularly to all animals for premedication. At 15 min after atropine administration isoflurane (Forane®)² was administered at an inspiratory concentra-

tion of 3-5% in group I, and sevoflurane (Sevorane®)³ was administered at an inspiratory concentration of 5-7% in group II, via a face mask during 15 min for the induction of anaesthesia. Endotracheal intubation was performed (average 1-3 min) in all cases at 15 min of induction period following the onset of general anaesthesia symptoms. After endotracheal intubation, the tube was connected to the inhalation anaesthesia device (AM832V Veteriner)⁴. To provide inhalation anaesthesia without excitation to all animals in both groups, the anaesthetic dose during the induction period was kept high at the beginning and the concentration of the anaesthetic was reduced after the appearance of deep anaesthesia symptoms. After the induction period, anaesthesia was continued at an inspiratory concentration of 1.5-3% in the isoflurane group and inspiratory concentration of 2.5-4% in the sevoflurane group. During the operation, the animals maintained spontaneous breathing, and 100% oxygen was used as the carrier gas in both groups.

During anaesthesia, the animals were monitored for physiological and clinical parameters, and the depth of anaesthesia was controlled by the presence of palpebral reflex, squeezing of the tail tip and interdigital space with Kocher forceps. The anaesthetic agent was cut off before the last few skin sutures were applied, and the spontaneous breathing of the animal was maintained with 100% oxygen. When the operation was completed, the anaesthetic device was disconnected from the endotracheal tube, and the animal was able to resume breathing normal atmospheric air. The endotracheal tube was removed with the onset of the swallowing reflex.

Collection of samples

Blood samples (10 mL each) were just taken before anaesthesia, just before skin incision, at the end of anaesthesia and surgery, and at the 24 h postoperatively. Blood of the calves was taken through a 1.0 × 32 mm diameter intravenous indwelling catheter placed in the left vena jugularis and collected in anticoagulated glass tubes. The samples were centrifuged at 6000 g for 10 min and the supernatant erythrocytes were removed with a pipette and the remaining plasma was placed in separate eppendorf tubes. Samples were stored at -80°C until analysis.

Biochemical analysis

Measurement of malondialdehyde (MDA) in plasma was done according to the method described by

Moreno *et al.* [24]. Briefly, the pink-colored complex formed as a result of MDA reaction with thiobarbituric acid was measured at 532 nm with a spectrophotometer (Model Shimadzu UV-1700)⁵.

Erythrocytes were washed 3 times with phosphate buffer and hemolyzed with cold bidistilled water [36]. The superoxide dismutase (SOD) activity in the erythrocyte hemolysates obtained was determined on the basis of nitroblue tetrazolium (NBT) reduction of superoxide radicals produced by the xanthine-xanthine oxidase system according to the method reported by Sun *et al.* [33]. The catalase (CAT) activity in erythrocytes was determined according to the method reported by Aebi [1]. According to this method, the absorbance decrease occurred during the decomposition of hydrogen peroxide (H₂O₂) into the water, and oxygen was measured spectrophotometrically at 240 nm. The glutathione peroxidase (GSH-Px) activity in erythrocytes, Lawrence *et al.* [22] was determined as stated. In the hemolysate, GSH-Px has oxidized with glutathione (GSH) cumene hydroperoxide (CHPO₄). As a color agent, the yellow color complex formed in the samples as a result of mixing with 5,5-dithiol-bis [2nitrobenzoic acid] (DTNB) solution was determined by the spectrophotometer at 412 nm.

Whole blood GSH concentration determined according to the method of Beutler [4]. Measurement of hemoglobin (Hb) was determined according to the cyanmethemoglobin method [9].

Statistical analysis

Statistical analysis of the data was performed using the SPSS (Statistical Package for Social Sciences)6 Windows 17 program. Descriptive findings were shown as mean ± standard deviation. Analysis for normal distribution was performed. In comparison between groups in statistically independent samples, t-Test conforming to the normal distribution in numerical (parametric) data, One Way ANOVA test, Kruskal Wal-

lis test for non-numerical (nonparametric) data, Mann Whitney U test, and Chi-square test for nominal data were used. Analysis of variance was used measures in the intergroup comparison. *P* < 0.05 was accepted as statistical significance value.

RESULTS

There was no significant difference between the 2 groups in point of age, weight, gender, time from induction to skin incision, and time from skin incision to the end of anaesthesia and surgery, duration of anaesthesia (Table 1).

In group I, MDA and antioxidant parameters SOD, CAT, GSH-Px, GSH did not show any significant change in their concentrations through the study (*P* > 0.05). In group II, MDA value decreased significantly before incision (*P* < 0.05), at the end of anaesthesia and surgery compared to the pre-anaesthesia value (*P* < 0.001), and then although it increased significantly at 24 h postoperatively, the value was still lower than the before anaesthesia level (*P* < 0.05). It was determined that SOD activity increased significantly after sevoflurane compared to pre-anaesthesia (*P* < 0.05), however, the increases in SOD activity detected during sevoflurane were not statistically significant. Through the study, a statistically insignificant increase was observed in the concentrations of CAT, GSH-Px, GSH compared to pre-anaesthesia (*P* > 0.05) [Table 2].

Before anaesthesia values of all measured biochemical parameters did not differ significantly between groups (*P* > 0.05). Before skin incision, at the end of anaesthesia and surgery, and at the 24 h postoperatively MDA was lower (*P* < 0.05) and SOD activity was higher (*P* < 0.05) than in group I in group II. There was no statistically significant difference just before skin incision, at the end of anaesthesia and surgery, and at the 24 h postoperatively, CAT, GSH-Px, GSH levels between the 2 groups (*P* > 0.05).

Table 1. Demographic data according to groups.

Parameter	Isoflurane group (I)	Sevoflurane group (II)
Age (week)	1.68 ± 1.14	1.70 ± 1.15
Weigh (kg)	40.50 ± 2.71	44.35 ± 2.74
Male/Female	3/4	2/5
Duration anaesthesia (min)	120 ± 8	115 ± 6
Time from induction.....	4 ± 1	3 ± 1
Time from skin incision.....	112 ± 8	110 ± 6

Time from induction to skin incision (min); Time from skin incision to end of anaesthesia and surgery (min). There were no significant differences between the 2 groups.

Table 2. Time dependent changes of lipid peroxidation and antioxidant parameters according to the groups.

Time	Groups [#]	MDA (μmol/L)	SOD (U/g-Hb)	CAT (k/g-Hb)	GSH-Px (IU/L)	GSH (μmol/g Hb)
Pre-induction	I	1.28 ± 0.11 ^a	115.21 ± 11.29 ^a	43.46 ± 7.23 ^a	27.98 ± 9.33 ^a	2.12 ± 0.13 ^a
	II	1.26 ± 0.10 ^a	112.13 ± 26.89 ^a	44.25 ± 6.78 ^a	29.16 ± 8.28 ^a	2.34 ± 0.11 ^a
Pre-incisional	I	1.18 ± 0.05 ^{a*}	120.15 ± 29.56 ^{a*}	44.66 ± 6.97 ^a	29.34 ± 10.33 ^a	2.49 ± 0.17 ^a
	II	0.45 ± 0.04 ^{b*}	169.53 ± 36.85 ^{b*}	53.69 ± 11.90 ^a	35.13 ± 6.25 ^a	3.84 ± 0.18 ^a
End of anaesthesia and surgery	I	1.22 ± 0.14 ^{a*}	135.35 ± 10.14 ^{a*}	45.34 ± 10.15 ^a	28.55 ± 8.87 ^a	2.55 ± 0.12 ^a
	II	0.16 ± 0.08 ^{c**}	173.41 ± 27.18 ^{b*}	61.17 ± 9.78 ^a	38.19 ± 7.21 ^a	3.81 ± 0.18 ^a
24-h postoperatively	I	1.30 ± 0.17 ^{a*}	140.44 ± 13.46 ^{a*}	44.92 ± 8.46 ^a	28.55 ± 8.87 ^a	2.73 ± 0.18 ^a
	II	0.48 ± 0.03 ^{b*}	178.99 ± 24.56 ^{b*}	65.27 ± 7.28 ^a	40.74 ± 9.23 ^a	3.90 ± 0.16 ^a

[#]Groups: Isoflurane (group I) & Sevoflurane (group II). Values are given as mean ± SE. ^{a-c}In the within-group comparison, there is a statistically significant difference between values with different letters in the same column ($P < 0.05$). ^{*}In comparisons between groups, there is a statistically significant difference between values with asterisks at the same time intervals ($*P < 0.05$; $**P < 0.001$).

DISCUSSION

Anaesthetic substances used in general anaesthesia and duration of anaesthesia are important factors that disrupt the immunological and antioxidant defense systems of the body, together with the stress caused by surgical trauma [5,13,16,21]. Some anaesthetic agents weaken the blood flow in the liver and cause oxidative stress and disruption of the antioxidant balance in animals [27,30]. Free radicals, which are the natural products of physiological activity in the body, try to keep the organism in a line that can be defined as “oxidant-antioxidant balance” with very sensitive equipment acquired from birth. The deterioration of this balance between oxidants and antioxidants, especially in favor of oxidants, is defined as oxidative stress and causes the disruption of the integrity of important vital structures of the cell such as membrane lipids, proteins, and DNA, and the development of pathological events in the living thing. The situation in which the oxidant / antioxidant balance is disrupted in favor of oxidants may result from the increase in the formation of free radicals or insufficient antioxidant activity [11,13,29,37,38]. Free radicals and reactive oxygen species, which are formed as a result of various enzymatic or chemical reactions in living organisms, can be formed during normal metabolism, as well as during the metabolism of some medications and foreign substances in the organism [13,14,25,26]. Enzymatic that can

metabolize free oxygen radicals of living organisms under normal conditions; there are SOD, CAT, and GSH-Px and non-enzymatic (vitamin A and E, GSH, beta carotene, uric acid) antioxidant defense systems. While SOD functions as a catalyst in the conversion of superoxide anions (O_2^-) to hydrogen peroxide (H_2O_2), the formed H_2O_2 ; it is eliminated by the CAT and GSH-Px enzymes. In addition, the GSH-Px enzyme is involved in the inhibition of other long-chain peroxides. GSH is an important intracellular antioxidant. Its oxidized form is involved in the inhibition of free radicals, stabilization of reduced sulfhydryl groups, and regeneration of tocopherol and ascorbate. It also acts as the cofactor of GSH-Px. Antioxidants are substances that help suppress the severity of oxidative stress by creating less active radicals or by reducing the damage of free radical chain reaction to proteins, lipids, carbohydrates, and DNA [11,37,38].

The malondialdehyde is a widely used parameter in the evaluation of lipid peroxidation caused by oxidative stress. Lipid peroxidation is a non-enzymatic chain reaction based mainly on the oxidation of unsaturated fatty acids, and increasing concentration of MDA in plasma is indicative of lipid peroxidation. By-products formed as a result of lipid peroxidation affect the properties of the cell membrane and the most common of these by-products is MDA. In particular, the erythrocyte membrane is rich in unsaturated fatty acids and is highly sensitive to lipid peroxidation [11].

Increase in intracellular calcium leads to an increase in xanthine oxidase, which increases the production of superoxide by activating proteases. Halothane, enflurane, and isoflurane are known to reduce calcium mobilization in a dose-dependent manner. It has been suggested that volatile anesthetics can reduce free radical production by this mechanism [25]. At the same time, inhalation anesthetics are said to cause an increase in oxidative cell damage by causing an increase in eicosanoids such as thromboxane and PGF1 alpha [32]. Durak *et al.* [8] found that nonenzymatic superoxide radical scavenger activity (NSSA), SOD, CAT levels decreased, MDA, oxidation resistance (OR) and GSH-Px levels increased in the renal tissue after isoflurane administration in pigs and they concluded that isoflurane had no antioxidant effect. Turkan *et al.* [35] investigated the effect of isoflurane on plasma and erythrocyte antioxidant enzymes and trace elements. While isoflurane does not affect plasma antioxidant enzymes (SOD and GSH-Px); it has been reported that it reduces erythrocyte SOD and GSH-Px activity and trace element levels. In the study of Pekcan *et al.* [28] investigating the effects on oxidative stress of isoflurane anaesthesia in Angora goats; investigated plasma MDA, vitamin A levels and erythrocyte SOD, CAT activities. As a result, they stated that isoflurane anaesthesia did not have a negative effect on blood MDA and measured antioxidant parameter levels in Angora goats. Similar to the findings of the researchers above, the changes in plasma MDA, and erythrocyte SOD, CAT, GSH, GSH-Px levels of isoflurane in the present study were not found to be statistically significant. According to the findings of this study, it was concluded that isoflurane has no negative effect on the oxidant system and antioxidant defense system.

Sevoflurane is an inhalation anesthetic that has entered clinical use in recent years. It provides rapid induction due to its low solubility in blood and tissues, and quick recovery since its low solubility in fat tissue. With this structure, it can be said that sevoflurane has the properties that should be found in the ideal anaesthetic [31,39,40]. However, its antioxidant effect is controversial in studies conducted with sevoflurane. Dikmen *et al.* [7] investigated the effects of desflurane and sevoflurane on free radicals that metabolize enzymes. In their study on rats, they did not give any agents to the control group (group I), they gave 2% sevoflurane + air / O₂ to group II, 6% desflurane + air

/ O₂ to group III, and 100% O₂ to group IV. They did this for 60 min for three days. SOD, CAT, GSH-Px, glutathion-s-transferase (GST) and thiobarbitiric acid reactive substances (TBARS) levels were measured in rats and they investigated their changes in electron microscopy. Although the electron microscopy changes were similar in the desflurane and sevoflurane groups, they observed that the levels of free radicals that metabolize enzymes increased in the sevoflurane group and caused more cell damage. Allaouchiche *et al.* [2], measured the levels of MDA, SOD, and GSH-Px in plasma and bronchoalveolar lavage during propofol, sevoflurane, or desflurane anaesthesia. During sevoflurane anaesthesia, there was no significant change in these parameters in both plasma and pulmonary lavage. In another study conducted by Dikmen *et al.* [6], they suggested that sevoflurane decreased the levels of antioxidant enzymes SOD and GSH-Px in humans, however, sevoflurane may protect erythrocytes against oxidative stress due to the increase in total antioxidant capacity. Lucchinetti *et al.* [23] sevoflurane was used in ischemia-reperfusion injury due to tourniquet, and they suggested that in healthy volunteers, sevoflurane (0.5-1% end-tidal) in sedative concentrations could be prevented from endothelial damage by preventing leukocyte activation and adhesion. In the present paper, similar to the results of the researchers [6,23], during sevoflurane, a statistically significant decrease in plasma MDA level, a statistically significant increase in erythrocyte SOD activity, an increase in erythrocyte CAT, GSH-Px and GSH levels, although not statistically significant, were observed. Decrease in plasma MDA level and increase in antioxidant parameters are thought to be due to the antioxidant effect of sevoflurane. Lastly, it was determined that isoflurane does not have a negative effect on the antioxidant defense system, whereas sevoflurane has an antioxidant effect of calves.

CONCLUSION

Excessive production of free oxygen radicals damages many biological materials such as protein, lipid, DNA and nucleotide, coenzymes in the organism. There is information that this damage promotes aging and also causes many diseases such as cardiovascular diseases, various types of cancer, cataracts, weakening of the immune system, and nervous system degenerative diseases. An important advantage of sevoflurane

compared to currently available anaesthetics is that it provides rapid induction due to its low solubility in blood and tissues, and rapid recovery due to its low solubility in fat. This feature is proof that the side effects of sevoflurane anaesthesia are minimal. In this regard, it is important to determine the effects of anesthetic agents used to create an ideal general anaesthesia on the oxidant and antioxidant defense system in the organism. The findings of the study show that sevoflurane exposure decreases lipid peroxidation and enhances antioxidant defense. The potential effect of sevoflurane on oxidative stress may lead to its preferred clinical use of sevoflurane compared to isoflurane.

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Ethical approval. The study was approved by The Animal Local Ethics Committee (KAÜ, HAYDEK Number: 2010-082), Kafkas University.

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

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