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Research Article

Effect of Propofol Induction on Antioxidant Defense System, Cytokines, and CD4+ and CD8+ T Cells in Cats

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Abstract

We investigated the effects of propofol on the antioxidant defense mechanisms, pro and anti-inflammatory cytokine expressions and specific defense processes in the study since these parameters play a significant role in postoperative complications, regulation of immune reactions, and wound healing. Twenty male cats were included in the study, anesthesia protocol was induced by IV administration of 6 mg/kg of propofol. Blood samples were harvested right before (T0) and fifteen minutes after (T1) propofol injection. Serum malondialdehyde (MDA), catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), IL-4, IL-8, TNF-α, IL-1β, and IFN-γ levels; the number of CD4+, CD8+ T cells and CD4/CD8 ratio in peripheral blood were determined. Propofol reduced the serum MDA and GSH-Px, while CAT and SOD levels remained unchanged. Furthermore, propofol did not impact serum IL-8, TNF-α, and IL-1β levels. Contrastingly, IFN-γ level tended to elevate, and serum IL-4 level was significantly increased. On the other hand, the CD8+ T cell population was significantly decreased, while the number of CD4+ T cells and the CD4/CD8 ratio were unaffected. Briefly, propofol did not adversely affect oxidative defense mechanisms, proinflammatory and anti-inflammatory cytokine cascade, and cell mediated immunity. Considering the insufficiency of cats' hepatic drug metabolism, we may conclude that propofol is a safe product regarding the investigated parameters.

Keywords: Antioxidant, Cat, Cytokine, Propofol, T cells

Introduction

Propofol (2,6-diisopropyl-phenol) is a sedative and hypnotic agent widely used to induce and maintain anesthesia in companion animals. It is favored in humans and animals due to the rapid induction of anesthesia, short action time, and fast elimination [1]. Propofol is mainly metabolized directly in the liver in humans, while, in cats, it is initially oxidized to 4-hydroxy propofol in the lungs and then eliminated due to the hepatic UDP-glucuronosyltransferase enzyme deficiency [2]. The relatively slow and inadequate extrahepatic metabolization of propofol impacts the cat's physiological status [3].

Oxidative stress is the impairment of the balance between antioxidants and free radicals in favor of the latter. It is reported that oxidative stress occurs because tissue perfusion and oxygenation changes during anesthesia [4]. In addition, feline erythrocytes are more prone to oxidative stress than other species due to relatively high concentrations of oxidizable sulfhydryl compounds. Particularly, repetitive anesthesia was indicated to have exerted oxidative damage in cats [3]. On the other hand, the antioxidant properties of propofol were shown in *in-vitro* and *in-vivo* studies conducted with humans and experimental animals [5]. Preoperative oxidative stress impacts postoperative wound healing, and its elevated levels play a role in potential complications. Therefore, considering the cats' susceptibility to oxidative stress, the potential effect of propofol on oxidative defense mechanisms is worth being investigated in this species.

Cytokines are small proteins that serve in inter-cellular signaling, regulating immune cells' development,

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proliferation, function, and survival, and thus, they play a crucial role in inflammation and infections. Cytokines are rapidly released in response to stimuli and tissue injury due to cytokine-encoding genes' fast-acting transcription and translation processes [6]; thus, short-term applications, like anesthesia, are highly likely to affect cytokine production. Changes in cytokine expression or impaired balance between pro and anti-inflammatory cytokines impact the efficacy of immune response and wound healing, exerting potential postoperative complications [7]. The potential effects of anesthetics on cytokine production have been evaluated in humans and experimental animals [8]. In cats, cytokine levels have been investigated during infectious and noninfectious inflammation [9]. Studies emphasizing the need for further exploration in cats solely focus on cytokine production during anesthesia.

This addition emphasizes the need for further research on cytokine production specifically during inflammation in cats. The function of T cells is highly significant since they are the fundamentals of the specific defense system, inducing both cytotoxic and antigen-producing activities benefiting the defense responses [10]. These cells are also closely associated with cytokines, since it is through cytokines that helper T cells are able to recognize the invading pathogen and present it to the specific defense system [11]. Therefore, cytokines and T cells should be simultaneously assessed while investigating the potential effects of anesthetics. The relevant connection was relatively investigated in humans [12]; however, few documented studies address the animal phenomenon [13]. Therefore, examining the effects of propofol anesthesia on cellular immune responses in cats would be beneficial.

The dispersion of propofol into the tissues and its metabolism and elimination is distinct in cats compared to dogs and other species [14]. This difference has the potential to alter the effects of anesthetics on the physiological system. However, more data are required concerning the issue in question. Therefore, this study was designed to reveal the potential effects of propofol on the cardiopulmonary system, antioxidant defense mechanisms, pro and anti-inflammatory cytokine expressions, and specific defense processes since all these parameters play a significant role in potential postoperative complications, regulation of immune reactions, and wound healing.

Material and Methods

Ethical Statement

This study was carried out with the permission of Istanbul University Local Ethics Committee (Approval no: 35980450-050.01.04). Additionally, informed consent forms were obtained from the owners.

Animals

Twenty cats that had to be operated on for various conditions were included in the study. The cats comprised 1-6-year-old males to rule out age and gender-associated variation *(Table 1)*. Of the cases in the study, 8 were castration, 2 were tooth extraction, 2 were blepharoplasty, 1 was urethrostomy, 1 was cystotomy, 1 was tibial fracture osteosynthesis, 1 was wound revision, 1 was removal of osteochondrodysplastic exostoses, 1 was femoral fracture osteosynthesis, 1 patient with inguinal cryptorchid, and 1 patient with enucleation underwent anesthesia.

Anesthesia

According to the American Society of Anesthesiologists (ASA) physical status classification system, ASA I and II patients were subjected to evaluations. All patients preoperatively underwent a routine physical exam, including hemograms and biochemical testing. Food and water intake ceased 6 h and 1 h before the induction of anesthesia, respectively. Each cat was administered IV 6 mg/kg of propofol through a 22 G angiocath (Vasofix; B. Braun Melsungen AG, Germany) inserted into the v. cephalica antebrachii.

Heart rate (HR), respiratory rate (fR), end-tidal CO_2 ($ETCO_2$), oxygen saturation (SpO_2), and body temperature were recorded before and during anesthesia. The heart

Table 1. *Demographic data of the cats included in the study*

Breed	n	Age (year)		Body Weight (kg)	
		Mean	SD	Mean	SD
Mixed breed	10	2.45	1.34	4.15	0.98
Scottish Fold	4	2.12	0.47	4.67	1.01
Exotic Shorthair	2	2	1.41	3.5	0.7
Persian cat	2	1.5	0.71	2.75	0.35
Siamese	1	4		4	
Norwegian forest cat	1	4		7	
Total	20	2.4		4.13	1.2

rhythm was monitored by a multifunctional ECG monitor (Advisor V9212 AR; Surgivet, Waukesha, WI, USA) based on lead II. The respiratory rate was initially determined by monitoring the chest movement and then the movements of the reservoir bag after endotracheal intubation.

The $ETCO_2$ levels were recorded by a capnometer integrated into the ECG monitor (Advisor V9212 AR; Surgivet, Waukesha, WI, USA), attached to the intubation tube. The SpO_2 was measured on the tongue mucosa using a pulse oximeter probe (Advisor V9212 AR; Surgivet, Waukesha, WI, USA). The body temperature was rectally taken by a digital thermometer (Omron, The Netherlands) during the anesthesia. Once the jaw muscles relaxed, endotracheal intubation was performed using appropriate-sized intubation tubes (Rüsch, Germany). General anesthesia was initiated by 4% and maintained by 2% isoflurane, after the blood draw at the 15th min following propofol induction (Royal-77 Anesthesia Machine CE 0434, Seul KOREA).

Blood Sampling

Blood samples were harvested through v. jugularis right before (T0) and 15 min after propofol administration prior to surgical incision (T1) and collected into anticoagulant and non-anticoagulant tubes for hemogram plus flow cytometry and to obtain sera stored at -80°C for further analyses, respectively.

Determining the Effect of Propofol on Antioxidant Levels

Serum malondialdehyde (MDA), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) levels were measured to assess the potential effect of propofol on oxidative defense mechanisms by the ELISA method using commercial kits specific to the cat (Abbkine Scientific, Hubei, China) according to the manufacturer's instructions.

Estimating the Effect of Propofol on Cytokine Expression Levels

Proinflammatory IL-8, IL-1β, TNF-α, and IFN and anti-inflammatory cytokines IL-4 were measured by the ELISA method using commercial kits specific to the cat (Abbkine Scientific, Hubei, China) according to the manufacturer's instructions. Briefly the stock solution (containing 400 ng/L cytokine) included in the kit was subjected to a series of dilutions by the sample diluent to obtain the standard solutions. In total, 150 µL of the former diluted solution was transferred to the latter in each dilution step, ensuring the final standard solutions contained a maximum assay concentration of 200 ng/L and minimum of 12.5 ng/L. Serum samples (50 µL) processed with the standard solutions were subjected to ELISA analysis according to the manufacturer's instructions. Absorbance measurements were taken at a wavelength of 405 nm using an RT6000 spectrophotometer (Rayto, Shenzhen, China). Intra- and inter-assay variabilities were determined to be <9% and <11%, respectively, based on information provided by the manufacturer.

Flow Cytometry Analysis

Cat-specific monoclonal CD3+ (CD3-FITC), CD4+ (CD4-PE), and CD8+ (CD8α-PE) antibodies (Southern Biotech© Birmingham, USA) were used to label T cells. Before the analyses, CD3-FITC and CD4-PE were diluted at a ratio of 1:50 and CD8α-PE at a ratio of 1:100 using PBS and stored at 2-8°C. Two flow cytometry tubes (12x75 mm, polystyrene) were prepared for each specimen, and 10 µL of CD3 FITC + CD4 PE and CD3 FITC + CD8 PE were pipetted into the tubes, respectively, and then 100 µL of whole blood was added into each tube. The tubes were vortexed at medium speed for 2 sec and left for 15 min-incubation in the dark, enabling the leukocytes to be stained with the antibodies. For removing the erythrocytes, 2 mL of the lysing solution was pipetted into each tube, which was vortexed and left to dark incubation for 10 min, centrifugated at 300 g for 5 min. The obtained supernatant was disposed of by a pipette. Then, 2 mL of PBS was added into the tubes, which were centrifuged again following the same procedure, and the supernatant was pipetted out. Finally, 500 µL of PBS was added into the tubes, and the specimens containing rinsed and monoclonal antibody-labeled leukocytes were read on the flow cytometer. The CellQuest program (Becton Dickinson, New Jersey. USA) was used for cytometric analysis. Twenty thousand cells per specimen were run through the flow cytometer, and CD4+ and CD8+ T cells were assessed by FL-1 and FL-2 detectors.

Statistical Analysis

The IBM SPSS Statistics Version 21 program (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. The Shapiro-Wilk test was applied to determine whether or not the data were normally distributed. The difference between the parameters regarding T0 (before anesthesia) and T1 (after anesthesia) and the normally distributed data of the paired specimens were analyzed by the dependent t-test. Non-normally distributed data were analyzed by the Wilcoxon Signed Rank test. The results were presented as mean ± standard error of mean (SEM) for parametric and median and inter-quarterly range (IQR) for non-parametric data. The significance was estimated at a level of $P<0.05$.

Results

The effects of propofol on the cardiopulmonary system and body temperature is presented in *Fig.1*.

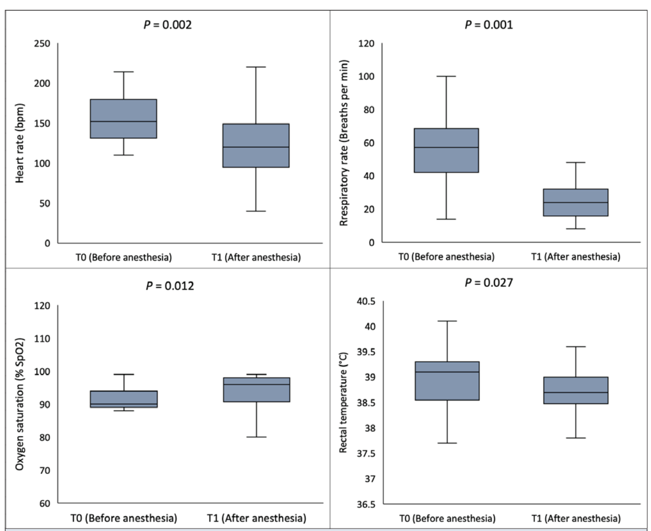

Fig 1. The effects of propofol on the cardiopulmonary system and body temperature. Data are presented by box plots where the central lines represent the median, and the whiskers represent the minimum and maximum values (n=20). Different letters above the columns indicate a significant difference between the groups, P<0.05 (n=20)

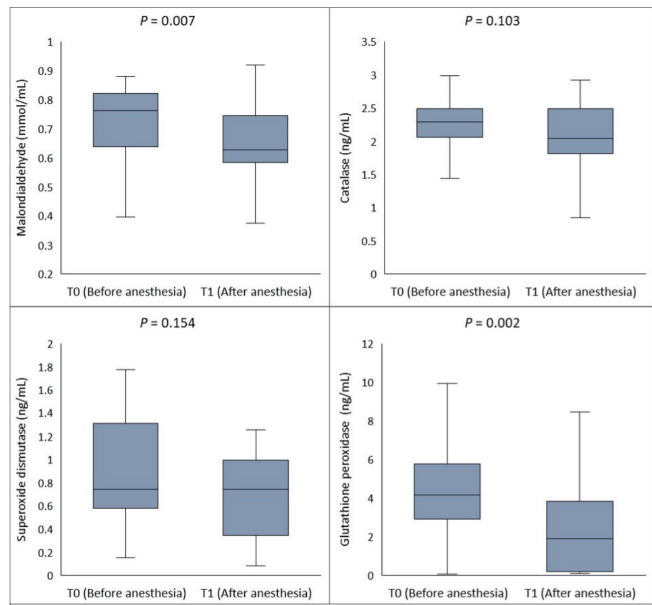

Fig 2. The effects of propofol on antioxidant defense responses. Serum malondialdehide (MDA), catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH-px) levels measured before sedation (T0) and 15 min after anesthesia induction (T1) in cats anesthetized with propofol. Data are presented by box plots where the central lines represent the median, and the whiskers represent the minimum and maximum values. Different letters above the columns indicate a significant difference between the groups, P<0.05 (n=20)

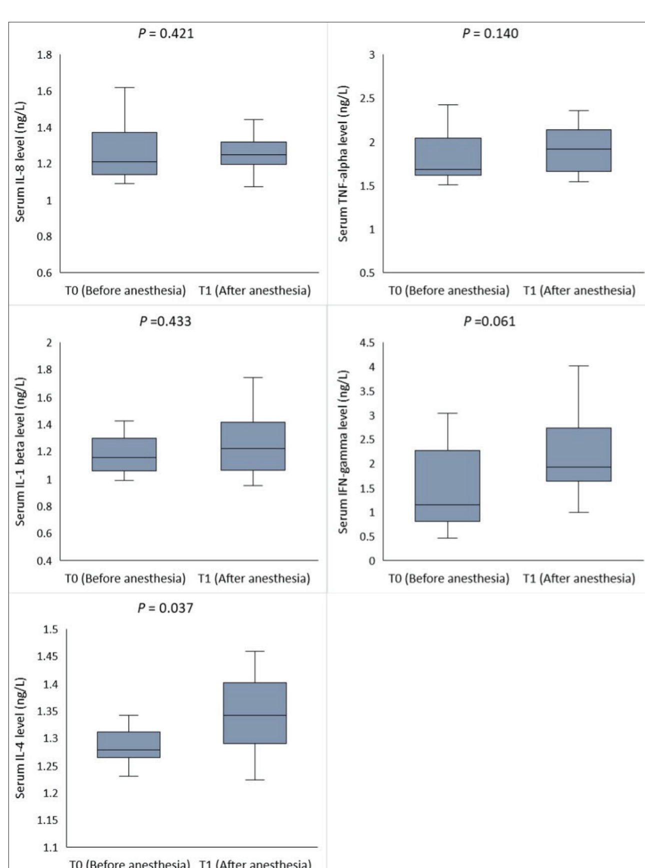

Fig 3. The effects of propofol on proinflammatory cytokines. Serum interleukin 8 (IL-8), tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1B), interferon gamma (IFN-G), and interleukin 4 (IL-4) levels before sedation (T0) and 15 min after anesthesia induction (T1) in cats anesthetized with propofol. Data are presented by box plots where the central lines represent the median, and the whiskers represent the minimum and maximum values. Different letters above the columns indicate a significant difference between the groups, P<0.05 (n=20)

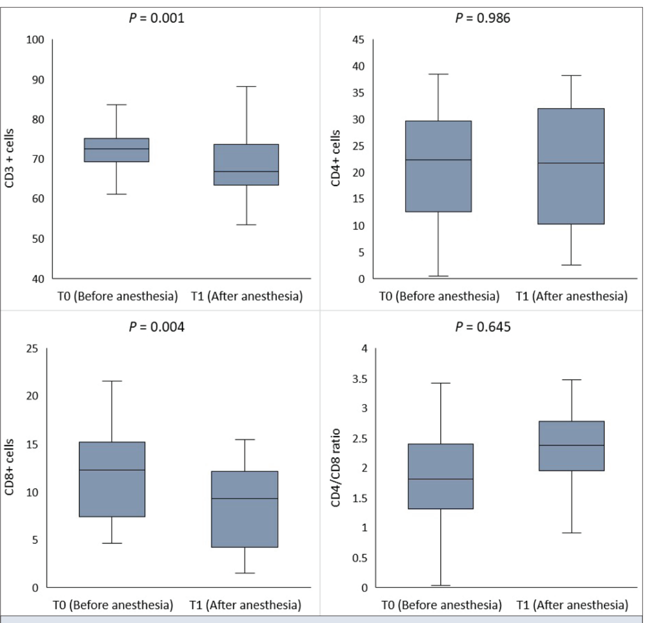

Fig 4. The effects of propofol on CD3+, CD4+, and CD8+ T cells. Peripheral blood CD3+, CD4+, CD8+ cells percentages and CD4/CD8 cell ratio before sedation (T0) and 15 min after anesthesia induction (T1) in cats anesthetized with propofol. Data are presented by box plots where the central lines represent the median, and the whiskers represent the minimum and maximum values. Different letters above the columns indicate a significant difference between the groups, P<0.05 (n=20)

The effects of propofol on antioxidant defense responses is presented in *Fig.2*. Serum MDA level was significantly decreased after propofol administration (P=0.007).

Likewise, serum GSH-Px level was also reduced (P=0.002). On the other hand, propofol did not affect serum CAT and SOD activities (P=0.103 and P=0.154, respectively).

The effects of propofol on proinflammatory cytokines is demonstrated in *Fig.3*. The data revealed no significant changes in serum IL-8, TNF-α, and IL-1β levels (P=0.421; P=0.140 and P=0.433, respectively). On the other hand, serum IFN-γ level was noted to have been increasing (P=0.061). Serum IL-4 level was significantly elevated after propofol anesthesia (P=0.037).

The effects of propofol on CD3+, CD4+, and CD8+ T cells is presented in *Fig.4*. The data revealed a significant decrease in CD3+ and CD8+ T cells (P=0.001 and P=0.004, respectively). In contrast, propofol anesthesia did not impact the number of CD4+ T cells and the CD4/CD8 ratio.

Discussion

Propofol leads to a dose-dependent decrease in systemic blood pressure, myocardial contractility, and cardiac output. Likewise, it was previously reported to have decreased the heart rate in rabbits [15]. On the other hand, documented studies indicated that dogs' heart rates remained unaffected [16]. In this study, unlike the dog, propofol anesthesia markedly decreased the heart rate in cats. Cats do not possess the UDP-glucuronosyltransferase enzymes found in humans and dogs, and they also lack conjugation enzymes such as N-acetyltransferase and thiopurine methyltransferase. The lack of these enzymes delays propofol's elimination [14], which was associated with a decreased heart rate in cats after propofol anesthesia.

IV administration of 6 mg/kg of propofol reduced the respiratory rate, and elevated the oxygen saturation in this study. In a previous study, the respiratory rate was similarly decreased, while, contrastingly, oxygen saturation remained unchanged in cats [17]. The increase in the SpO_2 level in our study was associated with the cats' intubation, followed by ventilation with 100% oxygen. A similar condition was previously reported in dogs anesthetized with propofol [16].

Hypothermia is a widely encountered complication of general anesthesia in small animal practice. In this study, hypothermia did not occur after propofol induction, yet, the body temperature was prominently decreased *(Fig.1)*. It was indicated that the body temperature was decreased by approximately 1.5°C in a short while in humans anesthetized with propofol [18]. Mild hypothermia [19] and unchanged body temperature [16], previously reported in dogs, were associated with the anesthetic dose.

Even though cats are quite susceptible to oxidative stress, few studies investigated this subject [20]. In this context, it is crucial to investigate the impact of propofol anesthesia on oxidative mechanisms. The MDA level is one of the biomarkers indicating oxidative stress in humans and animals, and an elevation in the MDA level points out oxidative stress. In previous studies, propofol anesthesia did not impact serum MDA levels in dogs [21]. On the other hand, propofol was reported to have reduced MDA levels in humans [22]. Our data revealed that propofol prominently reduced serum MDA levels, thus preventing oxidative stress. It is unlikely to elucidate the underlying mechanism thoroughly; nevertheless, propofol chemically resembles certain antioxidants such as α-tocopherol, butylated hydroxytoluene, and butylated hydroxyanisole. It was suggested that propofol neutralizes free radicals like the relevant antioxidants due to their chemical similarity [23], which was associated with our study's decrease in the MDA levels.

In the study, it was an intriguing finding that GSH-Px levels were decreased despite no increase in the MDA level, which raises the question of why the GSH-Px level decreased even though oxidative stress did not occur. A similar finding was previously demonstrated in humans, indicating that propofol reduced GSH-Px activity in the platelets by 28.3% [24]. Extensive oxygen exposition increases mitochondrial ROS production, and 2% of the oxygen entering the mitochondria emerges as ROS [25]. In the study, oxygen saturation was significantly elevated due to oxygen application through intubation, which was considered to be associated with the over-production of reactive oxygen molecules in the mitochondria, depleting the GSH-Px enzyme participating in the elimination of oxidative radicals. It was previously reported that the GSH-Px enzyme is abundant in the mitochondria and plays a significant role in eliminating the ROS that emerged [26]. Conclusively, the decrease in GSH-Px level was not associated with propofol but with the oxygen source administered.

The main function of superoxide dismutase (SOD) is to accelerate the dismutation of superoxide anion into hydrogen peroxide and molecular oxygen [27]. In our study, the serum SOD level remained unchanged in the cats anesthetized with propofol. No data are available revealing the effect of propofol anesthesia on the serum SOD level, hampering the comparison of our findings. Nevertheless, some documented studies previously indicated that the serum SOD level was not impacted either in dogs [16].

It was noted in the study that propofol did not affect proinflammatory cytokines other than IFN-γ, of which level tended to elevate after anesthesia *(Fig.3)*. It was reported in humans that, after propofol induction, when the cells in the whole blood cultures were stimulated by lipopolysaccharides (LPS), a significant increase was recorded in IFN-γ secretion [8]. Similarly, propofol

increased IFN-γ production in lymphocyte [12], macrophage, and natural killer cell cultures [28]. However, unlike the mentioned *in-vitro* studies, propofol revealed a decrease in IFN-γ production in dogs [16]. Therefore, *in-vitro* studies must be supported by in-vivo research. The issue is more critical in cats since immune cellular or inflammatory responses differ from those of other species [29]. In this study, the data from previous *in-vitro* studies conducted with humans were clinically verified in cats. IFN-γ is crucial in coordinating non-specific immune processes, antigen presentation to the specific defense system, and lymphocyte-endothelial cell interactions [30]. IFN-γ is one of the major stimulants activating inactive macrophages [31]. Furthermore, it increased the cellular proliferation and maturation in the injured tissues of mice [32]. *In-vitro* studies showed that IFN-γ accelerated wound healing by supporting the injured tissues' repair in the defective areas [33]. Therefore, we consider that the IFN-γ level's tendency to increase during anesthesia might efficiently prevent postoperative infections and improve wound healing.

Propofol was shown to exert anti-inflammatory effects in humans [34], which was previously associated with the inhibition of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8 [7]. Likewise, it was demonstrated that propofol inhibited TNF-α production in the type-II alveolar epithelial cells [35]. We may deduce that propofol also elicited an anti-inflammatory effect in cats. However, we assume propofol revealed such an effect not by inhibiting proinflammatory cytokines such as TNF-α or IL-1β but by increasing the anti-inflammatory cytokine IL-4's secretion.

The main source of IL-4 is T helper 2 (Th2) cells, a subtype of helper T cells [36]. When stimulated by various factors, helper T cells differentiate into Th1 and Th2 cells [37]. The transformation of T cells into Th2 and, thus, IL-4 secretion is inhibited by the leukocyte function-associated antigen-1 (LFA-1) [38]. Propofol has been shown to inhibit LFA-1 in humans [39]. Therefore, it was hypothesized that propofol may have increased IL-4 secretion in cats by abolishing LFA-1's inhibition on Th2 cells. Additionally, the inhibition of LFA-1 by propofol might also explain the tendency for increased production of IFN-γ. This is because Th1 cells, which are inhibited by LFA-1, are one of the main sources of IFN-γ [40]. Propofol's annihilation of the inhibitory activity of these cells might have increased the IFN-γ production.

Besides IL-4's inhibitory effect on proinflammatory cytokine expressions, it stimulates B cell activation and proliferation, which plays a role in antibody-mediated immune response [41]. The increase in the IL-4 level after propofol anesthesia was considered an affirmative output due to the restriction in potential postoperative infection and stimulation of antibody-mediated humoral immunity against potential risk for contamination.

Anesthetic agents are known to cause immunosuppression [42] and affect the subtypes of T lymphocytes [43]. In this study, no changes were recorded in CD4+ T cells and CD4+/CD8+ ratio; however, a significant decrease was detected in CD8+ T cells *(Fig. 4)*. Similarly, propofol induction in humans with lung cancer decreased CD8+ T cells, while CD4+ T cells remained unchanged [44]. No change was noted in the CD4+/CD8+ ratio in the patients with mammary cancer [45], which was compatible with our findings. It was reported in dogs that CD4+ and CD8+ T cells in the peripheral blood were decreased within a short time after propofol induction, yet they returned to their preoperative status after a while [13]. In the same study, the CD4+/CD8+ ratio remained unchanged, which was compatible with our findings.

CD8+ T cells are freely distributed between the blood circulatory system and the secondary lymphoid organs under homeostasis [46]. Expression of specific molecules on T and endothelial cells changes during infection or inflammation due to simultaneous effects of cytokines expressed and the antigenic agents, which impacts the CD8+ T cells' transfer from blood vessels to the tissues and from the tissues to the lymphoid organs and lymphoid vessels [47]. In this study, the decrease in CD8+ T cells in the peripheral blood vessels after propofol anesthesia might be associated with these cells' increased migration to the tissues since the cardinal molecule affecting the CD8+ T's transition from the blood vessels into the tissues is L-selectin expressed on the endothelial cells [48]. Propofol, along with remifentanil, is known to induce L-selectin expression [49]. Furthermore, in our study, the IFN-γ level's tendency to elevate after propofol induction might have increased CD8+ T cells' transfer to the tissues. It was also previously reported in an experimental model that when the IFN-γ-knockout mice received recombinant IFN-γ, vascular cell adhesion molecule-1 (VCAM-1) expression on cerebral blood vessels was increased, which stimulated the CD8+ T cells' transition into the tissues [50].

Anesthetic agents such as fentanyl, thiopental, and isoflurane were reported to have increased CD8+ T cells in the peripheral blood [43], suggesting that, unlike propofol, these anesthetics did not stimulate the mechanisms mediating cell migration from the blood vessels to the tissues. Regardless of the underlying mechanism, the decrease in the ratio of circulatory CD8+ T cells due to their transfer to the tissues is not considered an adverse event since naïve CD8+ T cells transferred to the tissues gain cytotoxic activity to directly demolish pathogen-infected cells and play a role in inflammatory cytokine production in the infection zone [47]. Therefore, they may offer drastic contributions to the host's defense responses in the postoperative period.

This study has some limitation. It was intended to evaluate the effects of propofol alone, without the effect

of isoflurane. Since we had to intubate the patient 15 min after giving a bolus dose of propofol, we were able to evaluate the effects of propofol after 15 min. In further studies, the effects of continuous infusion of propofol on cytokines and T cells can be evaluated.

The data obtained in the study revealed the suppressive effect of propofol anesthesia on the cardiorespiratory system in cats, which necessitates monitoring patients with heart conditions. Propofol also reduces body temperature; therefore, precautions should be taken against the potential risk of hypothermia during the surgery. Propofol did not adversely affect the antioxidant enzymes; on the contrary, it exhibited anti-inflammatory properties by reducing the MDA level and increasing IL-4 secretion. Furthermore, it did not negatively impact the cells of the specific defense system in the peripheral circulation.

In conclusion, propofol may enhances postoperative wound healing, reduces potential infection, and supports immune defense responses since it does not adversely impact the oxidative defense system, inflammatory/anti-inflammatory mechanisms, and cells of the specific defense system. Considering the cats' unique hepatic drug metabolism, propofol might be safely administered in this species regarding the investigated parameters.

Declarations

Availability of Data and Materials: The data that support the findings of this study are available from the corresponding author (E. Ergen) upon reasonable request.

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