

INFLUENCE OF SEVOFLURANE OR PROPOFOL ANAESTHESIA ON OXIDATIVE STRESS PARAMETERS IN DOGS WITH EARLY-STAGE MYXOMATOUS MITRAL VALVE DEGENERATION. A PRELIMINARY STUDY

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The aim of this study was to investigate the effects of total intravenous anaesthesia with propofol and anaesthesia induced with propofol and maintained with sevoflurane on oxidative stress parameters in dogs with early-stage myxomatous mitral valve degeneration (MMVD). Sixteen client-owned dogs with early stage MMVD that required periodontal treatment were included in the study. After induction with propofol, anaesthesia was maintained with propofol (group P) or sevoflurane (group PS). Blood samples for determination of vitamin E, superoxide dismutase, glutathione peroxidase and malondialdehyde were collected before premedication, 5 and 60 minutes and 6 hours after induction to anaesthesia. There were no significant differences between groups in any of the oxidative stress parameters at each sampling time. Compared to basal values, vitamin E concentration decreased significantly during anaesthesia in both groups and glutathione peroxidase activity increased 60 minutes after induction to anaesthesia in PS group. Anaesthesia with propofol or with propofol and sevoflurane did not have any significant impact on oxidative stress parameters in dogs with early stage MMVD. In terms of oxidative stress, both protocols may be equally safely used in dogs with early stage MMVD.

Key words: dogs, myxomatous mitral valve disease, oxidative stress, propofol, sevoflurane

INTRODUCTION

General anaesthesia as well as certain procedures performed under general anaesthesia can promote the formation of reactive oxygen species (ROS) in men [1] and in dogs [2]. These highly reactive compounds can react with lipids, carbohydrates, nucleic acids and proteins. Numerous antioxidant mechanisms exist in the body to counteract

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the effects of ROS. However, when endogenous antioxidants are consumed due to enhanced ROS formation, oxidative stress can occur [3]. Oxidative stress is known as an accompanying and determining factor in various diseases, including cardiovascular diseases in men [4] and dogs [5].

In clinical practice, procedures under general anaesthesia are often performed in dogs with cardiovascular diseases. The most common acquired cardiac disease in adult dogs is the myxomatous mitral valve degeneration (MMVD) [6]. Anaesthesia of these dogs may increase oxidative stress [7] and possibly aggravate their cardiac disease [5].

The combination of propofol as an induction agent and sevoflurane as a maintenance agent is one of the most commonly used anaesthetic protocols in dogs [8]. Propofol is an alkylphenol with a phenolic hydroxyl group, similar to vitamin E, which protects cellular membranes from lipid peroxidation, acting as a ROS scavenger [9]. Sevoflurane is a halogenated inhalation anaesthetic with a low degree of metabolism [10], but it is believed to enhance ROS production through its metabolism [11] and by altering mitochondrial bioenergetics [12].

The aim of this study was to investigate the effects of total intravenous anaesthesia with propofol alone or anaesthesia induced with propofol and maintained with sevoflurane on selected parameters of oxidative stress (vitamin E, antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px)) and the lipid peroxidation product malondialdehyde (MDA) in dogs with MMVD undergoing a dental procedure due to periodontal disease. We hypothesized that anaesthesia with propofol, which is believed to have antioxidant properties, causes less oxidative stress compared to anaesthesia with propofol and sevoflurane.

MATERIALS AND METHODS

Animal design

Sixteen client-owned dogs with MMVD, 5 females (1 neutered, 4 intact) and 11 males (3 neutered, 8 intact), median weight 13.4 kg (from 7.0 to 31.7 kg), median age 9 years (from 5.1 to 15.2 years), requiring dental treatment due to periodontal disease and receiving no medications at least 30 days before anaesthesia were included in the study. Dogs that fulfilled the inclusion criteria had no history of chronic systemic diseases such as allergies, chronic nephropathies, endocrinopathies, hepatopathies, neoplastic diseases, infectious diseases and/or heart failure.

Health status of dogs was determined by history, physical examination and the results of routine haematological and serum biochemical analyses (data not shown). A cardiology examination including auscultation of the heart and a complete echocardiographic examination (Vingmed System Five and VIVID E9; General Electric Healthcare, USA) was performed prior to anaesthesia. All dogs were classified as either class B1 or B2 according to the guidelines of the American College of Veterinary Internal Medicine (ACVIM) classification [13].

All procedures complied with applicable governmental regulations and informed client consent was obtained before the dogs entered the study. The study protocol was evaluated and approved by the National Ethics Committee. Informed consent has been obtained for client-owned animals included in this study.

Experimental protocol

The dogs were fasted 12 hours prior to anaesthesia, but given water *ad libitum* until premedication. Dogs were premedicated with morphine (0.3 mg/kg subcutaneously; Morphine Chl, Alkaloid Skopje, FYROM) and 15 minutes later preoxygenated for 5 minutes. Subsequently, the dogs were induced to anaesthesia with propofol (3 – 6 mg/kg intravenously; Norfol, Norbrook Laboratories Ltd, Northern Ireland), intubated endotracheally and allowed to breathe oxygen spontaneously using a circle breathing system. Dogs were randomly assigned to one of the two groups: in group P (8 dogs), anaesthesia was maintained with continuous intravenous administration of propofol (0.3 – 0.6 mg/kg/min), and in group PS (8 dogs) anaesthesia was maintained with sevoflurane (Sevorane; Abbott Laboratories, UK) at an end-tidal concentration of 2 – 3%. Hartmann's solution (5 ml/kg/hour intravenously; B Braun, Melsungen AG, Germany) was infused during anaesthesia. When indicated, analgesia was supported with ketamine (0.5 mg/kg intravenously; Narketan, Vétoquinol GmbH, Germany) and/or regional nerve blocks with levobupivacaine (1 – 2 mg/kg; Chirocaine, AbbVie, Italy). Perioperative antibiotic management was carried out with cefazolin (20 mg/kg intravenously; Cefamezin, Krka, Slovenia) if clinically indicated.

End-tidal sevoflurane concentration, end-tidal CO₂ tension, arterial oxygen saturation measured with pulse oximetry and respiratory rate were continuously monitored during anaesthesia with multiparametric anaesthesia monitor (RGM 5250; Ohmeda, USA). Heart rate was measured using a three-channel electrocardiograph (lead II) (M7000 Portable Vet Monitor; Guangdong Biolight Meditech, China). Blood pressure was measured indirectly with the use of an ultrasonic Doppler flow monitor (model 811; Parks Medical Electronics, USA).

Detailed oral and dental examination (probing and charting) and full-mouth dental radiographs were performed in all dogs to evaluate the extent and severity of periodontal disease and/or any other dental disease. Only dogs with the majority of teeth present were included in the study. For statistical analysis purposes, dogs were divided into two groups regarding their oral/dental disease: dogs with 25% or less and dogs with more than 25% of the teeth affected with periodontitis and/or dental fractures. All dogs underwent a dental procedure as clinically indicated [14].

Dogs were administered Hartmann's solution at 2 ml/kg/hour intravenously post-operatively and morphine 0.3 mg/kg subcutaneously every three hours when clinically indicated. Six hours after induction (i.e., after the last blood sampling) all dogs received carprofen (4 mg/kg intravenously; Rimadyl, Orion Pharma Animal Health, Sweden).

The dogs were discharged to home care the same evening, with analgesics and antibiotics prescribed depending on the extent of the dental disease/procedure.

Blood sample collection, processing and analyses

Blood samples (6 mL at each sampling) were collected before premedication, 5 minutes after induction, 60 minutes after induction and 6 hours after induction to anaesthesia.

Venous blood samples for the determination of plasma vitamin E (2 mL), GSH-Px activity in whole blood and SOD activity in erythrocyte lysate (2 mL) were collected in lithium heparin containing tubes (Vacuette, Greiner Bio-One, Austria) and for determination of plasma MDA (2 mL) in EDTA containing tubes (Vacuette, Greiner Bio-One, Austria).

Blood samples for determining vitamin E and MDA were immediately centrifuged at $1500 \times g$ for 15 minutes at 4°C . Plasma was separated and immediately frozen at -80°C until analysis. Aliquots of heparinised whole blood for the determination of GSH-Px activity were prepared and immediately frozen at -80°C until analysis. Haemolysed red blood cells for determination of SOD activity were prepared immediately after blood collection, following the manufacturer's instructions and stored at -80°C until analysis. Haemoglobin concentration in red blood cell haemolysates was determined spectrophotometrically by the cyanmethaemoglobin method using an RX-Daytona automated biochemistry analyser (RX-Daytona, Randox, UK).

Determination of vitamin E concentration in plasma

The procedure is based on analytical methods described elsewhere [15,16]. The concentration of vitamin E was determined by high performance liquid chromatography (HPLC) with fluorescence detection, using an external standard of alpha-tocopherol (Sigma, USA). The HPLC system (Waters Alliance 2695, Waters, USA) was equipped with an mBondapak C18 column, 10 mm, 3.9 x 300 mm and a Waters 474 fluorescence detector (Waters, USA). The calibration curve was linear in the tested concentration range (1–60 mg/L). The limit of quantification was 0.24 mg/L, the mean recovery was 102% and the inter-day coefficient of variability was 7%.

Determination of MDA concentration in plasma

Plasma samples for total MDA were derivatized with 2, 4-dinitrophenylhydrazine [17] and assayed using liquid chromatography coupled with tandem mass spectrometry. The MDA derivative was analysed using the Agilent 1290 Infinity HPLC coupled to an Agilent 6460 Triple-Quadrupole mass spectrometer equipped with a JetStream™ electro-spray-ionization source (Agilent Technologies, USA). The method was linear from 0.156 to 10 $\mu\text{mol/L}$ with the lower limit of quantification 0.156 $\mu\text{mol/L}$. The method was accurate (all deviations $\leq 12.9\%$) and precise (coefficient of variability $\leq 10.1\%$ intra-day and $\leq 12.1\%$ inter-day).

Determination of whole blood GSH-Px and erythrocyte SOD activities

Activities of GSH-Px and SOD were determined spectrophotometrically with an automated biochemical analyser (RX-Daytona, Randox, UK) using the commercially available Ransel and Ransod (Randox, UK) kits, respectively. Activities of GSH-Px and SOD were expressed as Units per gram of haemoglobin (U/g Hgb).

Statistical analysis

Statistical analysis was performed using R Statistical Software (version 3.2.2) (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>) with the nlme package [18]. Differences in the baseline characteristics of the two groups were evaluated by the Mann-Whitney test or Fisher exact test, when appropriate. A linear mixed-effect analysis was used to examine the treatment effect and trends over time. The models included a random intercept for each dog and three fixed effects: time, group and interaction term. In the case of significant interaction, multiple comparisons were done using Holm-Bonferroni correction. Post-hoc power analysis was performed with commercial software (SPSS 22.0, USA) using the general linear model/univariate approach. The value of $p < 0.05$ was considered statistically significant.

RESULTS

All sixteen dogs completed the study. The anaesthetic procedure lasted from 75 minutes to 185 minutes (median 117.5 minutes). Samples were successfully obtained and analysed and results statistically evaluated for vitamin E, MDA and SOD in all dogs. We encountered technical problems with latent fibrin formation in the samples for determination of haemoglobin concentration, which is needed for the activity of whole blood GSH-Px standardization. The samples with latent fibrin formation were excluded from the study and the results on GSH-Px reported for 7 dogs in the PS group and 4 dogs in the P group.

There were no significant differences between the two groups regarding oral/dental disease, administration of antibiotics, ketamine and regional nerve blocks. There were no significant differences in age of dogs and duration of anaesthesia between groups. The values of vitamin E, MDA, GSH-Px and SOD at each sampling time are reported in Table 1.

Table 1. Values (mean \pm SD) of vitamin E (Vit E), malondialdehyde (MDA), glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD)

| Parameter | Group | No. of dogs | Basal values | 5 min | 60 min | 6 h |
|-----------------------------|-------|-------------|--------------------|------------------------------|-------------------------------|------------------------------|
| Vit E ($\mu\text{mol/L}$) | PS | 8 | 67.1 \pm 27.5 | 62.3 \pm 26.2 | 60.5 \pm 26.0 ^b | 63.5 \pm 26.6 |
| | P | 8 | 69.0 \pm 15.8 | 63.5 \pm 16.2 ^a | 60.7 \pm 15.3 ^b | 61.7 \pm 19.3 ^b |
| MDA ($\mu\text{mol/L}$) | PS | 8 | 5.26 \pm 0.90 | 5.55 \pm 0.73 | 5.58 \pm 1.09 | 6.33 \pm 1.34 |
| | P | 8 | 6.03 \pm 0.67 | 5.99 \pm 1.12 | 5.83 \pm 0.83 | 6.01 \pm 0.83 |
| SOD (U/gHb) | PS | 8 | 2402.5 \pm 165.1 | 2403.4 \pm 180.2 | 2418.9 \pm 191.1 | 2407.6 \pm 200.6 |
| | P | 8 | 2142.3 \pm 306.9 | 2148.0 \pm 347.9 | 2221.0 \pm 390.6 | 2219.2 \pm 411.7 |
| GSH-Px (U/gHb) | PS | 7 | 427.4 \pm 38.9 | 443.1 \pm 36.2 | 477.2 \pm 42.6 ^c | 441.1 \pm 40.4 |
| | P | 4 | 461.8 \pm 78.3 | 477.2 \pm 72.1 | 469.4 \pm 86.5 | 465.7 \pm 72.6 |

PS – dogs anaesthetized with propofol and sevoflurane, P – dogs anaesthetized with propofol, a – significantly different from basal values ($p < 0.05$), b – significantly different from basal values ($p < 0.01$), c – significantly different from basal values ($p < 0.001$), No – number; min – minutes; h – hours.

Vitamin E concentration was significantly lower 5 minutes after induction in group P ($p < 0.05$), 60 minutes after induction in both groups ($p < 0.01$) and 6 hours after induction in group P ($p < 0.01$) in comparison to basal values.

GSH-Px activity was significantly higher 60 minutes after induction in comparison to basal values in group PS ($p < 0.001$). No significant changes in GSH-Px activity were observed in the P group. In addition, there were no significant changes in SOD and MDA values during anaesthesia in either group at any sampling time.

Statistical analyses showed no significant differences in vitamin E, GSH-Px, SOD and MDA values between the groups at any sampling time.

DISCUSSION

The present study revealed no significant differences in the selected oxidative stress parameters with the use of total intravenous anaesthesia with propofol or propofol/sevoflurane anaesthesia in dogs with early stage MMVD that underwent a dental procedure due to periodontal disease. To the authors' knowledge, this is the first study to look into the effects of general anaesthesia on oxidant and antioxidant status in dogs with MMVD.

Although propofol, which is chemically similar to endogenous vitamin E, has been reported to have antioxidant properties [19], no such effects could be confirmed from this study, and total intravenous anaesthesia with propofol alone was not found to be superior to propofol/sevoflurane anaesthesia in this regard. The plasma concentration of vitamin E decreased after induction to anaesthesia in the propofol group and during anaesthesia in both groups, which might be a consequence of vitamin E consumption due to increased production of ROS during anaesthesia [20]. Naziroğlu and Günay

[21] also reported a significant decrease in serum vitamin E concentrations in healthy dogs anaesthetized with enflurane. Our results are in general agreement with the results of the study of Ceylan et al. [22] carried out in men. They compared the effects of propofol and desflurane on serum vitamin E concentrations and, similarly to our study, observed no significant difference between the two groups.

In our study, MDA concentrations were not significantly altered in either group, suggesting that the two anaesthetic protocols used here did not increase lipid peroxidation process. Yarsan et al. [23] also found no significant difference in MDA concentration between dogs anaesthetized with halothane or isoflurane. Allaouchiche et al. [24] aimed to evaluate the oxidative stress in porcine bronchoalveolar lavage fluid and blood after exposure to desflurane, sevoflurane and propofol. Contrary to our study, plasma MDA concentrations were significantly lower in pigs exposed to propofol, whereas no significant changes were observed after sevoflurane exposure. In a recent study in men, Akin et al. [25] evaluated serum levels of MDA, GSH-Px, selenium, copper, zinc and iron after exposure to sevoflurane, propofol or desflurane. Sevoflurane and propofol anaesthesia decreased MDA concentrations and increased GSH-Px activity significantly.

The interpretation of our results on GSH-Px may be difficult because of the loss of samples assayed due to technical problems. In our study, GSH-Px activity was significantly higher in group PS 60 minutes after induction, but there was no significant difference between the two groups. In the study of Allaouchiche et al. [24], GSH-Px activity was significantly higher in the propofol group, whereas sevoflurane did not significantly change GSH-Px activity.

As expected, anaesthesia maintained with propofol or sevoflurane in our study did not significantly alter SOD activity as stated in previous studies in men [22] and swine [24]. Superoxide dismutase is a highly regulated enzyme which is believed to be involved in cellular signalling and adaptation pathways [26].

This study has certain limitations, especially with regard to the results on GSH-Px and low number of dogs included in the study. Moreover, non-significant differences obtained in this preliminary study may be the result of insufficient statistical power [27]. Post-hoc power analyses between groups indicated low power coefficients (less than the recommended 0.80) [27] for all oxidative stress parameters at each sampling time, which suggests ambiguity. Post-hoc power analyses within individual groups, PS and P respectively, also demonstrated low power coefficients for MDA, SOD and GSH-Px in PS and P groups, and for vitamin E in PS group.

The dogs were client-owned; therefore, environmental and nutritional variables were not standardised, although the dogs did not receive any additional vitamin supplements at least one month prior to anaesthesia. The dental procedures and the use of additional drugs varied depending on the clinical case in order to provide the best professional care for the dogs; however, the list of medications used was restricted. The strict

inclusion criteria limited the number of dogs that were available for inclusion in this study.

Within the limitations of the study, our results indicate that both, anaesthesia induced with propofol and maintained with sevoflurane or total intravenous anaesthesia with propofol have similar effects on oxidative stress parameters in dogs with early stage MMVD. However, the results of this preliminary study warrant further investigation on a larger group of dogs including other oxidative stress parameters and/or a control group of healthy dogs.

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Authors' contributions

TK performed experiments (anaesthesia) and prepared the manuscript. NSA was responsible for the conception and design of the research, analysed the samples and revised the manuscript. NA performed the experiments (dentistry) and has been involved in drafting the manuscript. PAD performed the experiments (cardiology) and has been involved in drafting the manuscript. VT analysed the samples and has been involved in drafting the manuscript. SA was responsible for the conception and the design of the study, edited and revised the manuscript. All listed authors have seen and approved the final version of the manuscript and all authors agree to the conditions outlined in the copyright assignment.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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UTICAJ SEVOFLURANA ILI ANESTEZIJE PROPOFOLOM NA PARAMETRE OKSIDATIVNOG STRESA KOD PASA SA MIKSOMATOZNOM DEGENERACIJOM MITRALNIH ZALISTAKA U RANOJ FAZI. PRELIMARNO ISPITIVANJE.

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Cilj studije je bio da se ispituju efekti potpune intravenske anestezije propofolom i anestezije indukovane propofolom i kasnije održavane upotrebom sevoflurana, na parametre oksidativnog stresa kod pasa kod kojih je postojala miksomatozna degeneracija mitralnih zalistaka, u ranoj fazi (MMVD). Studija je obavljena na 16 pasa poznatih vlasnika koji su svi bili u ranoj fazi MMVD, a kojima je obavljen periodontalni tretman. Posle indukcije anestezije propofolom, anestezija je nastavljena ili propofolom (grupa P) ili sevofluranom (grupa PS). Uzorci krvi za određivanje E vitamina, superoksid dismutaze, glutation peroksidaze i malondialdehida, uzimani su pre medikacije, 5 i 60 minuta kao i 6 sati posle indukcije anestezije. Nije bilo značajnih razlika između

grupa u bilo kom parametru oksidativnog stresa, u bilo koje vreme uzimanja uzoraka. Upoređivanjem sa bazalnim parametrima, koncentracije E vitamina su se značajno smanjivale tokom anestezije u obe grupe, a aktivnost glutathion peroksidaze je povećana 60 minuta posle indukcije anestezije u PS grupi. Anestezija sa propofolom i anestezija sa propofolom i sevofluranom, nije imala ikakav efekat na parametre oksidativnog stresa kod pasa u ranoj fazi MMVD. U odnosu na oksidativni stres, oba protokola mogu bezbedno da se koriste kod pasa u ranoj fazi MMVD.