

TARGET-CONTROLLED INFUSION OF PROPOFOL INDUCES SIGNIFICANT HYPERTRIGLYCERIDEMIA IN HEALTHY DOGS UNDERGOING ELECTIVE ORCHIECTOMY

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This study assessed serum triglyceride (TG) concentrations during target-controlled infusion (TCI) of propofol in healthy dogs undergoing elective orchiectomy and investigated the association between propofol infusion rate and serum TG concentrations. Eight male healthy dogs (14.8 ± 12.5 kg; median age 13.5 months; ASA I) were premedicated with acepromazine 0.05 mg/kg and morphine 0.4 mg/kg intramuscularly. Anesthesia was induced and maintained with propofol TCI targeting 7.0 µg/mL for 40 minutes. The primary outcome was serum TG concentration at four timepoints: TB (baseline), TIND (immediately after intubation), TINF20 (20 min), and TINF40 (40 min). Sample size was calculated a priori for 90% power. Statistical analysis was performed using the Friedman test followed by Dunn's multiple-comparison test, with $P < 0.05$. All animals completed the protocol without adverse events. TG concentrations increased significantly from baseline [47 (30-73) mg/dL] to TIND [182 (100-227) mg/dL; $P = 0.023$], TINF20 [255 (132-733) mg/dL; $P = 0.016$], and TINF40 [293 (141-395) mg/dL; $P = 0.008$]. Hypertriglyceridemia (>112 mg/dL) occurred in 6/8 dogs (75.0%) after induction and 8/8 (100.0%) at 20 minutes. Infusion rate decreased 15.7% ($0.51 \pm 0.06 \rightarrow 0.43 \pm 0.03$ mg/kg/min). No significant correlation was detected between propofol infusion rate and serum TG concentrations ($r = 0.12$; $P = 0.54$). However, the study is underpowered to evaluate potential associations, and further

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research is needed. Propofol TCI produces early and marked increases in triglyceride concentrations in healthy dogs even during short procedures. These findings suggest interindividual variability in triglyceride response, but causality cannot be inferred.

Keywords: anesthesia; canine; hypertriglyceridemia; lipemia; propofol; target-controlled infusion

INTRODUCTION

Total intravenous anesthesia (TIVA) has been employed in veterinary medicine for various procedures in dogs [1-3]. Propofol is a widely used intravenous anesthetic agent [2,3]. This drug is characterized by rapid induction, predictable recovery, and short half-life after single-dose administration or continuous infusion [3]. Propofol (2,6-diisopropylphenol) is formulated as a lipid emulsion containing 10% soybean oil, giving it a milky appearance and isotonicity with plasma [4,5]. Its mechanism of action involves potentiation of inhibitory neurotransmission mediated by GABA-A receptors, resulting in neuronal hyperpolarization [6,7], with possible secondary action on glutamatergic NMDA receptors [8,9].

Despite its pharmacodynamic advantages, the lipid composition of propofol has been associated with hypertriglyceridemia in different species. Studies have documented triglyceride elevation after prolonged infusion in humans [10-12] and rabbits [13]. Recently, Chagas et al. [14] reported the first study in dogs, demonstrating a significant triglyceride increase after induction (median 120 mg/dL) with progression up to 90 minutes of infusion (median 229 mg/dL), using a mean rate of 0.44 ± 0.09 mg/kg/min. Notably, 80.0% of animals exceeded the reference value of 112 mg/dL at the end of infusion [15], but there was no correlation between administered doses and magnitude of increase [14].

A potential strategy to optimize propofol administration is target-controlled infusion (TCI), which uses pharmacokinetic models to calculate and automatically adjust infusion rates necessary to achieve predetermined target plasma concentrations [16-21]. The pharmacokinetic model for dogs developed by Cattai et al. [22] demonstrated consistent induction with concentrations of $5.5 \mu\text{g/mL}$ ($4\text{--}6.5 \mu\text{g/mL}$) and maintenance with a mean rate of 0.3 ± 0.1 mg/kg/min. Additionally, an experimental study in dogs demonstrated satisfactory performance and clinical applicability of propofol TCI [19]. Although TCI offers greater pharmacokinetic precision compared to conventional infusion, its impact on lipid metabolism remains unknown.

To our knowledge, no study has evaluated triglyceride levels during propofol TCI in dogs. The absence of dose-response correlation with conventional infusion [14] suggests that quantification of infusion rate alone may not adequately capture drug exposure and its metabolic response. Therefore, this study aimed to evaluate serum triglyceride levels during propofol TCI in healthy dogs undergoing elective orchiectomy, investigating the correlation between propofol infusion rates and measured triglycerides. The primary outcome was serum triglyceride concentration;

secondary outcomes included cardiovascular and ventilatory parameters, temperature, and propofol infusion rate. We hypothesized that propofol TCI induces significant triglyceride elevation even during short procedures.

MATERIAL AND METHODS

Ethical approval

This study was approved on May 20, 2025, by the Animal Use Ethics Committee (CEUA) of the Federal University of Santa Maria (protocol number 4732170225).

Reporting guidelines

This study was designed and reported according to ARRIVE 2.0 guidelines (Animal Research: Reporting of In Vivo Experiments) [23,24] for in vivo research and SAMPL (Statistical Analyses and Methods in the Published Literature) [25] for reporting statistical methods.

Animals

Eight healthy male dogs were used, referred to the University Veterinary Hospital for elective orchiectomy during the period from June to July 2025. Inclusion criteria were: (1) age between 6 months and 6 years; (2) body weight between 5 and 40 kg; (3) absence of abnormalities on complete physical examination (heart rate, respiratory rate, rectal temperature, capillary refill time, mucous membrane color, hydration status, abdominal palpation, and cardiopulmonary auscultation); (4) complete blood count within reference limits for the species; (5) serum biochemical analysis within reference values for urea (21-60 mg/dL), creatinine (0.5-1.5 mg/dL), alanine aminotransferase (10-88 U/L), and alkaline phosphatase (20-150 U/L); (6) baseline triglycerides within reference range (20-112 mg/dL); (7) baseline cholesterol within reference range (135-270 mg/dL) [15]; (8) absence of history of metabolic, hepatic, pancreatic, or cardiovascular disease; (9) ASA I classification (American Society of Anesthesiologists); and (10) written informed consent obtained from the owner.

Exclusion criteria were: (1) abnormalities detected in preoperative examinations; (2) history of adverse reactions to sedative, tranquilizing, or anesthetic drugs; (3) use of medications that interfere with lipid metabolism in the 30 days prior to the procedure; (4) inadequate fasting; and (5) anesthetic complications during the procedure.

Recruitment and allocation

Nine animals were initially screened for the study. Of these, one was excluded before inclusion due to non-attendance on the scheduled day for the surgical procedure. The eight included animals completed the protocol without complications, resulting in n

= 8 for all analyses. There was no randomization, as the study consisted of a single observational treatment without comparison groups. No control group was included because the objective was to describe the temporal intrasubject variation of serum triglycerides during anesthesia with propofol (TCI), in a longitudinal repeated measures design in which each animal served as its own control (TB, TIND, TINF20, and TINF40). The experimental unit was the individual animal (dog). The four triglyceride measurements per animal (TB, TIND, TINF20, TINF40) were treated as repeated measures of the same individual, not as independent samples.

Sample size calculation

Sample size was determined a priori using G*Power 3.1.9.2 (Heinrich-Heine-Universität Düsseldorf, Germany), based on data from Chagas *et al.*¹⁴ who reported triglycerides of 36 mg/dL (after premedication) and 229 mg/dL (90 minutes) with a standard deviation of approximately 80 mg/dL. Using analysis of variance for repeated measures with four timepoints, effect size $f = 0.85$, correlation between repeated measures $r = 0.5$, power of 90% ($1 - \beta = 0.90$), and significance level $\alpha = 0.05$ (two-tailed), a minimum n of eight animals was obtained. All eight animals completed the protocol without losses, resulting in $n = 8$ for analysis of all outcomes (serum triglycerides, physiological parameters, and propofol infusion rates).

Preparation of animals

All animals underwent the same fasting protocol consisting of 8 hours of food withholding and 1 hour of water withholding before anesthesia. On the day of the procedure, they remained in a preparation room (22-24°C, natural lighting, low noise) for at least 30 minutes before premedication, accompanied by a team member, without active restraint, and without visual access to the owner.

Anesthetic protocol

Premedication consisted of acepromazine 0.05 mg/kg (Acepran®, Vetnil, São Paulo, Brazil) and morphine 0.4 mg/kg (Dimorf®, Cristália, São Paulo, Brazil) administered intramuscularly. After 15 minutes, trichotomy, antisepsis, and establishment of venous access in the cephalic vein with a 22G catheter (BD Angiocath™, Becton Dickinson, São Paulo, Brazil) were performed.

Anesthetic induction was performed with a target-controlled infusion pump (SDA403, SDAMed, Campinas, Brazil) programmed with the Cattai *et al.*²² model for dogs, using 1% propofol (Propovan®, Cristália, São Paulo, Brazil). The target plasma concentration was set at 7.0 µg/mL based on the Cattai *et al.* [22] model (induction range 4-6.5 µg/mL). This slightly higher target was chosen because the present study used only phenothiazine and opioid (without $\alpha 2$ -adrenergic agonists used in 54% of Cattai's animals) and animals lacked prior hospital acclimatization.

Induction was considered complete when the animal exhibited loss of the palpebral reflex, ventromedial rotation of the eyeball, and adequate mandibular relaxation for orotracheal intubation. After intubation with an appropriate endotracheal tube (Solidor, Recife, Brazil), the cuff was inflated and the tube connected to the breathing circuit.

Anesthetic maintenance was performed with continuous propofol infusion through the TCI pump, maintaining a target plasma concentration of 7.0 µg/mL for 40 minutes. Animals were maintained under pressure-cycled mechanical ventilation (VentPet, RZ Vet, Belo Horizonte, Brazil), with respiratory frequency and inspiratory pressure adjusted to maintain EtCO₂ between 35–45 mmHg, using FiO₂ of 100%.

For intraoperative analgesia, bilateral intratesticular block was performed with 2% lidocaine without epinephrine (Xylestesin®, Cristália, São Paulo, Brazil), dose of 0.05 mL/kg per testicle, and prescrotal block of the incision line with 0.1 mL/kg of 2% lidocaine without epinephrine, performed 5 minutes before incision. All surgeries were performed by the same experienced team.

Blood sampling and laboratory analysis

Four venous blood samples (3 mL each) were collected at the following timepoints: baseline (TB), before premedication; TIND, immediately following orotracheal intubation; TINF20, at 20 minutes of infusion; and TINF40, at 40 minutes of infusion, all by jugular venipuncture. To minimize potential confounding factors, the following were standardized: operating room, team and equipment (including TCI pump), fasting/water, ventilation, ambient temperature (22–24°C), and the order of collections (TB→TIND→TINF20→TINF40).

Serum was obtained by centrifugation of whole blood collected in tubes without additives, at 900 × g for 5 minutes. Serum triglyceride concentration was determined by colorimetric enzymatic method, using an automated biochemical analyzer (BioClin® 2000 Plus, Belo Horizonte, Brazil) and specific commercial reagents (BioClin®, Brazil). Analyses were always performed by the same professional to minimize technical variability.

Anesthetic monitoring

Animals were continuously monitored (multiparameter monitor SDAMed 8B, Campinas, Brazil) with records every 5 minutes: heart rate, arterial pressure (oscillometry), respiratory rate, EtCO₂ (capnography), SpO₂ (oximetry), esophageal temperature, and propofol infusion rate. Anesthetic depth was assessed through absence of palpebral reflexes, ventromedial ocular position, mandibular relaxation, and absence of response to nociceptive stimuli.

Animal welfare and interruption criteria

During anesthesia, welfare was monitored by physiological parameters, absence of response to nociceptive stimuli, and maintenance of adequate depth. During recovery, animals were observed until they achieved: temperature $\geq 37^{\circ}\text{C}$, quadrupedal position, responsiveness to stimuli, and absence of discomfort, being monitored every 10 minutes until discharge. All subjects received postoperative analgesia (metamizole 25 mg/kg and meloxicam 0.2 mg/kg IV administered immediately after extubation) in addition to the intraoperative block. Discharge occurred on the same day after complete recovery.

Predefined criteria for protocol interruption included: (1) difficulty maintaining anesthetic depth with the established target concentration of 7 $\mu\text{g/mL}$, either due to under – or overdose; (2) hemodynamic instability (mean arterial pressure < 60 mmHg, systolic arterial pressure < 90 mmHg, or need for intervention with fluid bolus and/or inotropes/vasopressors); (3) cardiac arrhythmias; (4) hypoxemia ($\text{SpO}_2 < 94\%$); (5) persistent hypercapnia ($\text{EtCO}_2 > 45$ mmHg); (6) serious adverse events related to the anesthetic or surgical procedure. No animal reached any of these criteria.

Statistical analysis

Normality was verified by Shapiro-Wilk test for each evaluation timepoint. For triglycerides, results were: Baseline ($W = 0.941$; $P = 0.619$), TIND ($W = 0.898$; $P = 0.278$), TINF20 ($W = 0.797$; $P = 0.026$), TINF40 ($W = 0.856$; $P = 0.109$). Given the violation of normality at TINF20 ($P < 0.05$) and the observed asymmetry in the data, nonparametric analysis for repeated measures was used (Friedman test followed by Dunn test with correction for multiple comparisons). Normal data were expressed as mean $\pm$ standard deviation and compared by ANOVA for repeated measures followed by Tukey test. Non-normal data were expressed as median (minimum-maximum) with 95% confidence intervals (95% CI). Correlations were analyzed by Pearson (parametric) or Spearman (nonparametric) correlation coefficient between propofol infusion rate and triglycerides. Correlation analyses were considered exploratory, and results should be interpreted cautiously because repeated measurements within the same animal may violate independence assumptions. Repeated-measures correlation approaches may be more appropriate in future studies. Effect size for Friedman test was calculated using Kendall's W . Analyses used GraphPad Prism 9.3.0 (GraphPad Software Inc., San Diego, CA, USA), with significance established a priori at $P < 0.05$. P values are reported exactly, with three decimal places and leading zero (e.g., $P = 0.032$); when < 0.001 , presented as $P < 0.001$. We avoided generic expressions such as ' $P < 0.05$ '. Confidence intervals (95% CI) for the primary outcome (serum triglyceride concentrations) and propofol infusion rate were calculated using the Baptista-Pike method implemented in GraphPad Prism 9.3.0. Secondary physiological variables are presented as measures of central tendency and dispersion, without 95% CI, as they only document anesthetic stability.

There were no missing data; all animals completed the protocol without losses. There was no blinding due to the observational nature of the study. The primary outcome was considered an objective and automated measure, with low risk of measurement bias.

RESULTS

Eight healthy male dogs were included, with mean weight of 14.8 ± 12.5 kg (5.6-37.8 kg) and median age of 13.5 months (9-89 months). The total propofol dose for induction was 5.1 ± 0.9 mg/kg (4.2-6.5 mg/kg), administered in an average of 5 minutes (5-6 minutes). Surgical time was 13 ± 1 minutes, total anesthetic time was 40 minutes, time to extubation was 14 ± 7 minutes, and time to achieve sternal recumbency was 47 ± 15 minutes. All eight animals completed the 40-minute protocol without adverse events and achieved complete recovery without need for additional interventions beyond standardized postoperative analgesia.

Physiological parameters and propofol infusion rates are presented in Table 1.

Table 1. Mean $\pm$ standard deviation or median (minimum-maximum) of physiological variables and propofol rate obtained from eight healthy dogs subjected to premedication with acepromazine and morphine and target-controlled infusion of propofol set at 7 μ g/mL over 40 minutes of anesthesia for elective orchiectomy.

Variable	Minutes							
	5	10	15	20	25	30	35	40
HR (bpm)	106 (95-137)	106 (90-156)	101 (96-133)	105 (95-127)	107 (97-126)	106 (95-115)	102 (96-112)	100 (93-110)
SAP (mmHg)	115 ± 33	115 ± 30	108 ± 9	108 ± 12	107 ± 14	107 ± 12	105 ± 13	108 ± 17
DAP (mmHg)	70 ± 32	69 ± 35	57 ± 12	57 ± 11	58 ± 12	62 ± 12	61 ± 11	62 ± 12
MAP (mmHg)	87 ± 30	89 ± 32	76 ± 12	75 ± 9	76 ± 10	78 ± 11	79 ± 11	81 ± 12
RR (bpm)	9 (7-9)	9 (7-10)	9 (8-10)	9 (8-10)	9 (8-10)	9 (8-10)	9 (8-10)	9 (8-10)
EtCO₂ (mmHg)	40 (36-44) ^{ab}	41 (37-43) ^{ab}	41 (37-45) ^{ab}	38 (36-44) ^{ab}	38 (36-44) ^{ab}	38 (35-43) ^{ab}	39 (35-42) ^b	38 (37-43) ^{ab}
SpO₂ (%)	98 ± 1	98 ± 1	98 ± 1	98 ± 1	98 ± 1	98 ± 1	98 ± 1	99 ± 1
ET (°C)	36.8 ± 0.9^a	36.7 ± 0.9^{ab}	36.6 ± 0.8^{abc}	36.05 ± 0.9^{bc}	36.4 ± 0.9^c	36.2 ± 0.9^d	36.0 ± 0.9^c	35.9 ± 0.9^f
Propofol (mg/kg/min)	0.51 ± 0.06^a	0.48 ± 0.04^{ab}	0.45 ± 0.03^b	0.45 ± 0.03^{bc}	0.44 ± 0.03^{bcd}	0.44 ± 0.03^{cd}	0.43 ± 0.03^{de}	0.43 ± 0.03^{de}

Different superscript letters represent significant differences between timepoints according to Tukey test (normal distribution) or Dunn test (non-normal distribution) ($P < 0.05$). **HR**, heart rate; **SAP**, systolic arterial pressure; **DAP**, diastolic arterial pressure; **MAP**, mean arterial pressure; **RR**, respiratory rate; **EtCO₂**, end-tidal carbon dioxide partial pressure; **SpO₂**, peripheral oxyhemoglobin saturation; **ET**, esophageal temperature.

Heart rate, systolic, diastolic, and mean arterial pressures remained stable throughout the procedure, with no significant differences between timepoints. Ventilatory parameters demonstrated adequate control during mechanical ventilation, with respiratory rate, EtCO₂, and SpO₂ remaining within physiological limits, confirming adequate oxygenation and ventilation. Esophageal temperature showed a progressive decline from 36.8°C to 35.9°C ($P < 0.05$), and propofol infusion rate demonstrated gradual reduction from 0.51 ± 0.06 mg/kg/min to 0.43 ± 0.03 mg/kg/min ($P < 0.05$), representing a 15.7% reduction (95% CI 11.4-23.5%) over 40 minutes. Higher variability in arterial pressure was observed during early post-induction measurements, likely reflecting interindividual responses during anesthetic induction.

Serum triglyceride concentrations increased significantly after propofol administration (Figure 1). Friedman's test demonstrated a significant effect of time on triglycerides ($\chi^2(3) = 21.75$; $P < 0.0001$), with effect size Kendall's $W = 0.906$, indicating very large magnitude. Baseline values were 47 (30-73) mg/dL [95% CI 32-61], rising to 182 (100-227) mg/dL [95% CI 106-220] at TIND ($P = 0.023$ vs baseline), 255 (132-733) mg/dL [95% CI 151-444] at TINF20 ($P = 0.016$ vs baseline), and 293 (141-395) mg/dL [95% CI 157-382] at TINF40 ($P = 0.008$ vs baseline).

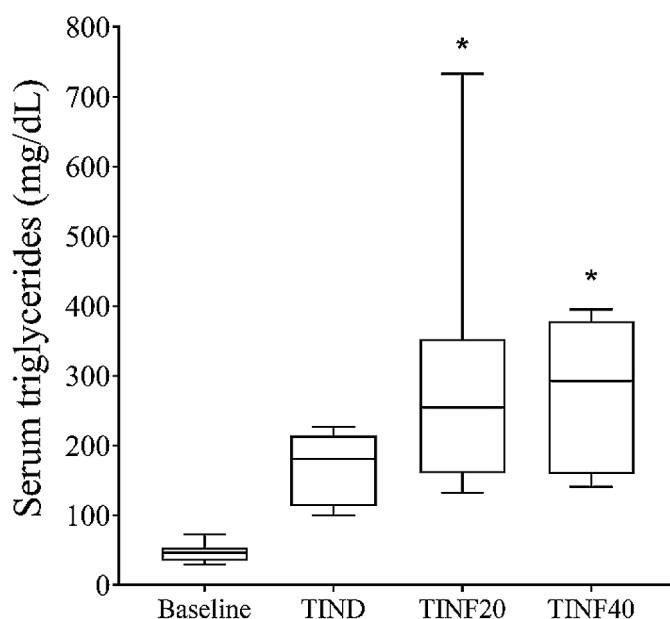


Figure 1. Serum triglyceride concentrations during target-controlled infusion of propofol in healthy dogs.

Legend: Serum triglyceride concentrations (mg/dL) in eight healthy dogs at baseline (TB), immediately after intubation (TIND), 20 minutes of infusion (TINF20), and 40 minutes of infusion (TINF40) during target-controlled infusion of propofol (target plasma concentration: 7.0 µg/mL). Data are presented as median, interquartile range, and minimum–maximum values. $P < 0.05$ versus baseline according to Dunn test.

Immediately after induction, 75.0% of dogs (6/8) exceeded the reference value of 112 mg/dL. At 20 minutes, all animals (8/8, 100.0%) presented hypertriglyceridemia, remaining above the reference interval throughout the 40-minute observation period. Triglycerides increased 286% (TIND), 443% (TINF20), and 522% (TINF40) versus baseline, with median absolute increases of +135 mg/dL (95% CI 64-171), +208 mg/dL (95% CI 121-420), and +246 mg/dL (95% CI 120-351), respectively. Considerable individual variability was observed (coefficient of variation 68% at TINF20), with range of 30-73 mg/dL at baseline and 132-733 mg/dL (range 601 mg/dL) at 20 minutes. Individual triglyceride trajectories are presented in Supplementary Figure S1, illustrating the marked heterogeneity of responses.

No significant correlation was detected between propofol infusion rate and triglycerides (Spearman coefficient $r = 0.12$; $P = 0.54$), nor between cumulative dose and magnitude of increase ($r = 0.08$; $P = 0.67$). However, the study is underpowered to evaluate potential associations, and these findings should be interpreted cautiously.

DISCUSSION

The present study demonstrates that target-controlled infusion of propofol induces significant hypertriglyceridemia in healthy dogs, even during short procedures (40 minutes). Triglycerides increased rapidly after induction, with continuous progression during anesthetic maintenance, resulting in hypertriglyceridemia in all animals at the end of the protocol.

These findings are consistent with Chagas *et al.* [14], who demonstrated hypertriglyceridemia in 80.0% of bitches during conventional propofol infusion (0.44 mg/kg/min, 90 minutes). That study reported triglycerides of 36 mg/dL (after premedication) to 229 mg/dL (90 min). In the present study, starting from 47 mg/dL, levels reached 293 mg/dL at 40 minutes with similar rates (0.51-0.43 mg/kg/min). Triglyceride concentrations at 40 minutes were numerically higher than those reported by Chagas *et al.* at 90 minutes. However, differences in study population, anesthetic protocol, and baseline characteristics preclude direct comparisons. Importantly, similar to that reported by Chagas *et al.* [14], the present study found no significant correlation between propofol infusion rate and the magnitude of hypertriglyceridemia ($r = 0.12$; $P = 0.54$). Although one of the objectives of this study was to investigate the association between propofol infusion rate and triglyceride concentrations, no significant association was detected. However, interpretation of this finding requires caution. In addition to the limited sample size, propofol infusion rates showed relatively little variation among animals due to the target-controlled infusion protocol, whereas triglyceride responses were heterogeneous. This combination may have reduced the ability to detect potential dose-response relationships. Therefore, the absence of a detected association should not be interpreted as evidence that propofol exposure is unrelated to triglyceride response. Larger studies including a wider range of propofol exposures are required to clarify whether triglyceride elevations are influenced primarily

by drug exposure, individual biological factors, or a combination of both. Despite the lack of a detected dose-response relationship, considerable interindividual variability was observed, as illustrated by the marked differences in triglyceride trajectories among animals in Supplementary Figure S1. These findings suggest heterogeneity in triglyceride response to propofol administration; however, the mechanisms underlying this variability were not investigated and causality cannot be established.

Seventy-five percent of animals exceeded the reference value immediately after induction and 100% at 20 minutes. This pattern suggests that even short procedures may be sufficient to induce marked lipid alterations, and monitoring may be warranted in at-risk patients (pancreatitis, pre-existing hyperlipidemia, hepatic disease). Additionally, hypertriglyceridemia developed more rapidly in the present canine population than reported in human ICU studies. However, this comparison should be interpreted cautiously, as differences in population characteristics, clinical status, and duration of propofol exposure limit direct interspecies comparisons [26–28].

Despite the pharmacokinetic precision of TCI [16,18], which automatically adjusts infusion rates, hypertriglyceridemia developed similarly to conventional infusion. Progressive rate reduction (0.51 to 0.43 mg/kg/min) reflects automatic adjustment to maintain stable target concentration [19]. This finding suggests that the metabolic response may be related to propofol exposure and its lipid emulsion formulation, regardless of the administration method. Although TCI offers pharmacodynamic advantages such as greater anesthetic plane stability and more predictable recovery, it does not mitigate the metabolic risk associated with propofol lipid emulsion.

The pathophysiological mechanisms of propofol-induced hypertriglyceridemia are multifactorial. Propofol contains 10% lipid emulsion (0.1 g/mL) [4,5], providing considerable exogenous lipid load. Proposed mechanisms include increased exogenous lipid load, mitochondrial dysfunction with blockade of fatty acid β -oxidation [13,29], interference with lipoprotein lipase activity, and increased hepatic synthesis of very low-density lipoproteins (VLDL) [29]. Ypsilantis et al. [13] demonstrated that propofol-induced hypertriglyceridemia exceeds that from lipid emulsion alone, suggesting direct metabolic effects.

The individual variability observed in this study was considerable (CV = 68%, range 132–733 mg/dL at T1N20), corroborating Chagas et al.'s [14] findings of absence of dose-response correlation. This variability is also evident in Supplementary Figure S1, where all animals exhibited increasing triglyceride concentrations over time, although with markedly different magnitudes of response. One dog reached 733 mg/dL at 20 minutes, a value close to the 862 mg/dL threshold associated with increased pancreatitis risk in Miniature Schnauzers [30,31] and exceeding 500 mg/dL values from which pancreatitis risk progressively increases in humans [32,33], although specific thresholds for intervention remain controversial, while another remained at 132 mg/dL despite similar rates. This heterogeneity may reflect genetic factors, enzymatic

polymorphisms, or differences in hepatic clearance, although these mechanisms were not investigated in the present study.

These findings, together with existing literature, suggest that caution may be warranted in dogs with metabolic disorders such as hyperlipidemia, diabetes mellitus, hepatic disease, obesity, hypothyroidism, or a history of pancreatitis [14,30-33]. In these patients, anesthetic strategies aimed at reducing propofol exposure, including inhalant anesthesia or balanced anesthetic techniques using adjuvant drugs may be considered. Likewise, triglyceride monitoring during prolonged propofol administration may be useful, particularly in animals with pre-existing metabolic disorders [14,30-33]. However, specific intervention thresholds for triglyceride concentrations remain speculative in veterinary medicine and require further investigation before clinical recommendations can be established.

The study presents important limitations. First, actual plasma propofol concentrations were not measured, precluding validation of TCI system accuracy. Although the model by Cattai *et al.* [22] demonstrated acceptable performance (median PE 3.1%), individual variations may have occurred. However, this study focused on clinical application of TCI, not pharmacokinetic validation. Second, the lack of a control group with inhalant anesthesia prevents differentiation between specific propofol effects and the anesthetic procedure *per se*. Although propofol is the most likely contributor to the observed triglyceride increases because of its lipid emulsion formulation, effects of anesthesia, surgical stimulation, and stress response cannot be excluded. Third, the population consisted exclusively of young male (median 13.5 months) and healthy (ASA I) subjects undergoing a short procedure (40 minutes), which limits external validity. Extrapolation requires caution for geriatric patients, with metabolic comorbidities (pancreatitis, diabetes, hyperlipidemia, obesity), and prolonged anesthesia. Fourth, additional lipid metabolism markers (cholesterol fractions, free fatty acids, lipase activity) and factors potentially influencing metabolism—including progressive hypothermia (36.8°C to 35.9°C) from absence of active warming and lack of prior hospital acclimatization—were not evaluated. Finally, sample size ($n = 8$), although calculated *a priori* as adequate to detect the primary outcome (90% power), presents limitations for precision estimates. The 95% CI were wide (151-444 mg/dL at T1N20) due to high variability (CV = 68%). However, similar findings were observed by Chagas *et al.* [14] ($n = 10$), although larger studies are necessary to better characterize potential associations between propofol exposure and triglyceride response.

Future studies should address identified limitations: (1) include actual plasma propofol measurement to validate TCI accuracy; (2) use controlled design with inhalant anesthesia group; (3) evaluate complete lipid profile to elucidate mechanisms; (4) investigate population with metabolic comorbidities; (5) determine post-anesthetic normalization time for triglycerides; (6) compare different propofol emulsions; (7) evaluate effect of propofol-sparing adjuvant drugs; and (8) conduct multicenter studies with larger number of animals to better characterize individual variability.

Target-controlled infusion of propofol induces significant hypertriglyceridemia in healthy dogs undergoing elective orchiectomy. Triglyceride elevation is rapid, with 75% of animals developing hypertriglyceridemia within 5 minutes, and remains progressive and marked even during short-duration anesthesia (40 minutes). Despite the pharmacokinetic precision of TCI, hypertriglyceridemia occurred consistently throughout the study period. The absence of a detected dose-response relationship may reflect interindividual variability, although causality cannot be established. These findings suggest that caution may be warranted when propofol is used in patients with metabolic comorbidities; however, further studies are required before definitive clinical recommendations can be established.

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Authors' contributions

FA and JCG conceived and designed the study, performed data collection and interpretation, conducted statistical analysis, and drafted the manuscript. LTM performed statistical analysis and contributed to manuscript preparation. LSV, GSO, JOO, LBG, ARS, RSS, EVO carried out data collection. CMA and GCF contributed to review and approval of final version of manuscript. BPF conceived and designed the study, performed data collection and analysis, conducted statistical analysis, contributed to manuscript writing, and performed English translation. AVS contributed to study design, supervised the project, and critically revised the manuscript.

Declaration of competing interests

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

Statement of informed consent

The owner understood procedure and agreed that results related to investigation or treatment of their companion animals, could be published in Scientific Journal *Acta Veterinaria-Beograd*.

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CILJNO KONTROLOSANA INFUZIJA PROPOFOLA IZAZIVA ZNAČAJNU HIPERTRIGLICERIDEMIJU KOD ZDRAVIH PASA PODVRGNUTIH ELEKTIVNOJ ORHIJEKTOMIJI

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Ova studija procenila je koncentracije triglicerida (TG) u serumu tokom ciljno kontrolisane infuzije (TCI) propofola kod zdravih pasa podvrgnutih elektivnoj orhiektomiji i ispitivala povezanost između brzine infuzije propofola i koncentracije TG u serumu. Osam zdravih mužjaka pasa ($14,8 \pm 12,5$ kg; medijana starosti 13,5 meseci; ASA I) premedikovano je acepromazinom (0,05 mg/kg) i morfinom (0,4 mg/kg) intramuskularno. Anestezija je indukovana i održavana TCI propofolom sa ciljnom koncentracijom od 7,0 $\mu\text{g/mL}$ tokom 40 minuta. Primarni ishod bila je koncentracija TG u serumu u četiri vremenske tačke: TB (bazalna vrednost), TIND (odmah nakon intubacije), TINF20 (20 min) i TINF40 (40 min). Veličina uzorka izračunata je unapred za snagu od 90%. Statistička analiza sprovedena je Friedmanovim testom praćenim Dunnovim testom za višestruka poređenja, uz nivo značajnosti $P < 0,05$. Sve životinje završile su protokol bez neželjenih događaja. Koncentracije TG značajno su porasle u odnosu na početne vrednosti [47 (30–73) mg/dL] na TIND [182 (100–227) mg/dL; $P = 0,023$], TINF20 [255 (132–733) mg/dL; $P = 0,016$] i TINF40 [293 (141–395) mg/dL; $P =$

0,008]. Hipertrigliceridemija (>112 mg/dL) zabeležena je kod 6/8 pasa (75,0%) nakon indukcije i kod 8/8 pasa (100,0%) nakon 20 minuta. Brzina infuzije smanjila se za 15,7% ($0,51 \pm 0,06 \rightarrow 0,43 \pm 0,03$ mg/kg/min). Nije utvrđena statistički značajna korelacija između brzine infuzije propofola i koncentracije TG u serumu ($r = 0,12$; $P = 0,54$). Međutim, studija nema dovoljnu statističku snagu za procenu potencijalnih povezanosti, te su potrebna dalja istraživanja. TCI propofola dovodi do ranog i izraženog porasta koncentracije triglicerida kod zdravih pasa čak i tokom kratkotrajnih procedura. Ovi nalazi ukazuju na individualnu varijabilnost u odgovoru triglicerida, ali se uzročna povezanost ne može zaključiti.