Hematological and Biochemical Effects of Total Intravenous Anaesthesia of Ketamine, Propofol and their Combinations in Mixed-Breed Dogs

Albert K. Felix[1] and Doreen G. Ndossi[1]

[1]*Department of Veterinary Surgery and Theriogenology, Sokoine University of Agriculture, Morogoro, Tanzania*

Corresponding author: albert.felix@sua.ac.tz

SUMMARY

This study assessed the effects of ketamine, propofol, and their combinations administered using total intravenous anaesthesia (TIVA) on hematological and biochemical indices in mixed-breed dogs. Ten adult dogs were given five different treatments in a repeated crossover experiment. Treatments were ketamine (KK) and propofol (PP) individually, and as a combination in 1:1 (KP1), 1:2 (KP2), and 1:3 (KP3) ketamine-to-propofol ratios. No statistically significant differences were observed in lymphocyte, neutrophil, monocyte, RBC, HCT, Hb, BUN, or creatinine levels among the five protocols, and lymphocyte, monocyte, and HCT values within protocols over 60 minutes. Statistical differences among protocols were noted in WBC ($p=0.002$), ALT ($p=0.047$), and AST ($p=0.012$). Within protocols, when pre-induction values were compared to post-induction, there was a significant decrease in WBC in KP3 at 30th ($p=0.009$) and 60th ($p=0.033$) minutes. A significant decrease in Hb in KP3 at the 60th minute ($p=0.049$) and a significant increase in neutrophil count in KP2 post-induction ($p=0.041$). Creatinine concentration significantly increased from the 30th to 60th minute ($p<0.001$). All other changes within groups were not statistically significant, but there was a general increase in BUN and a decrease in WBC, monocytes, RBC, HCT, Hb, and AST in all groups post-induction. Due to the decrease in red blood cell counts, hematocrit, and hemoglobin concentration observed in all groups, it is imperative to diligently monitor animals, especially those that are immunocompromised, and ensure a patent airway when ketamine, propofol, or ketamine + propofol TIVA protocols are to be used.

Keywords: TIVA; ketofol; CRI; hematology; biochemistry

Article History

Submitted: 9 June 2026
Revised: 21 October 2026
Accepted: 27 October 2026
Published: 29 October 2026

Tanzania Veterinary Journal Vol. 41(2)2026
https://doi.org/10.4314/tvj.v41i2.14
ISSN: 0856 - 1451 (Print)
ISSN: 2714-206X (Online)
https://tvj.sua.ac.tz

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INTRODUCTION

Total Intravenous Anaesthesia (TIVA) is a practice of administering drugs for induction and maintenance of anaesthesia strictly through the intravenous route without the need for any inhalation agents (Campbell *et al*., 2001). The method often involves anaesthetic induction by administering a bolus dose aimed at achieving the required blood concentration of the anaesthetic drug, followed by maintenance dose either by intermittent boluses, Constant Rate Infusion (CRI) or Target-Controlled Infusion (TCI) (Waelbers *et al*., 2009). Advantages of TIVA over inhalant anaesthesia include reduced risk of exposure to volatile anaesthetic agents for both the practitioner and the environment, hence reduced greenhouse effect (Zeng and Cheng, 2021), less immunosuppression to the anaesthetized patient (Mahmoud and Ammar, 2011), and its affordability as it requires less sophisticated and expensive equipment (Saikia *et al.*, 2022).

TIVA commonly uses anaesthetic drugs with rapid onset of action, metabolism, and clearance from the body, such as propofol (Ambros *et al.,* 2008). Propofol has, however, been associated with dose-dependent decreased cardiac output, reduced arterial blood pressure, and poor analgesia (Smith *et al.,* 1993). The drug has shown compatibility with ketamine, which has a cardio-stimulatory effect, hence counterbalancing cardiovascular depression (Celestine *et al.,* 2014).

Some anaesthetic drugs are shown to affect hemato-biochemical dynamics of animals. The effects include the oxidant-antioxidant state of cells responsible for immunity, such as lymphocytes. Oxidative stress may result in cellular damage and an increase in apoptosis, which may predispose to postoperative lymphocytopenia and immunological deficits (Delogu *et al.,* 2004).

There is limited information available on the haematological and biochemical effects of ketamine and propofol alone or in combination administered through TIVA in mixed-breed dogs. Reports on several mixed and officially recognized breeds have also revealed breed-specific metabolic and physiological peculiarities that could affect drug pharmacokinetics and pharmacodynamics across breeds (Fleischer *et al*., 2008).

This study assessed some of the hematological and biochemical effects of ketamine and propofol individually, but also as a combination administered through TIVA in mixed-breed dogs.

MATERIALS AND METHODS

Ethical clearance

Written approval of the study was obtained from the Research Ethics Committee of Sokoine University of Agriculture at the Directorate of Research, Technology Transfer and Consultancy (reference number SUA/DPRTC/R/186/VOLIII).

Experiment set-up

Ten apparently healthy dogs of either sex with a mean body weight of 13 ± 2.7 kg received five different treatments i.e., Ketamine (KK) and Propofol (PP) individually, and Ketofol at 1:1 (KP1), 1:2 (KP2) and 1:3 (KP3) in a repeated crossover experiment. Each treatment was administered twice to improve consistency since we opted to use a smaller sample size for ethical reasons. There was a one-week interval between treatments of the same protocol, and a two-week washout period before the animals received a different treatment.

Study animals

The inclusion criteria were apparently healthy male and female dogs in American Society of Anesthesiologists (ASA) category I or II, aged between 2-4 years. Health status was determined through clinical history, physical examination, and laboratory examination when necessary. Exclusion criteria were very young or old age, pregnancy/lactation, aggressiveness, animals undergoing any form of therapy, and those with signs/symptoms of disease. The dogs were kept for at least two weeks at the College of Veterinary Medicine and Biomedical Sciences (CVMBS), Sokoine University of Agriculture (SUA) kennels for acclimatization, health examination, deworming and vaccination prior to commencement of the study. They were fasted for 12 hours but provided with water ad libitum until 3 hours before anaesthetic induction.

Anaesthesia induction and maintenance

Premedication comprising 0.04 mg/kg atropine (Swiss Parenterals LTD®, India) and 2 mg/kg

Xylazine (Interchemie®, Netherlands) was administered via the intramuscular route on the semitendinosus muscle. Once fully sedated, the animals were moved to a surgical table and placed on sternal recumbency for catheterization and induction, then later maintained in left lateral recumbency. An 18-gauge cannula was inserted into the cephalic vein of one limb for administration of the anaesthetic agents.

The animals received five different treatments to cover Ketamine (KK) and Propofol (PP) individually, and Ketofol at 1:1 (KP1), 1:2 (KP2), and 1:3 (KP3). Each treatment was repeated twice. Anaesthetic induction was through a single bolus slow intravenous administration, and maintenance through constant rate infusion using a burette infusion set (Neomedic®, United Kingdom) with a drop factor of 60. The ketofol mixture was aseptically reconstituted to make a total volume of 60 mL that was delivered for 60 minutes and not used beyond one hour. Final concentrations of preparations were intended to deliver drugs at constant pre-determined infusion rates.

In the KK group, induction was achieved by 5 mg/kg ketamine, and maintenance was through 0.3 mg/kg/min for one hour. In the PP group, induction was achieved by 5 mg/kg propofol and maintenance was through 0.3 mg/kg/min for one hour. In the KP1 group, induction was achieved by 4 mg/kg ketofol (i.e., 2 mg of ketamine + 2 mg of propofol per kg body weight), and maintenance was through 0.3 mg/kg/min for one hour (i.e., 0.15 mg/kg/min propofol and 0.15 mg/kg/min ketamine).

In KP2, induction was achieved by 4 mg/kg ketofol (i.e., 1.3 mg of ketamine + 2.6 mg of propofol per kg body weight), and maintenance was through 0.3 mg/kg/min for an hour (0.1 mg/kg/min ketamine and 0.2 mg/kg/min propofol). In KP3, induction was achieved by 4 mg/kg ketofol (i.e., 1 mg of ketamine + 3 mg of propofol per kg body weight), and maintenance was through 0.3 mg/kg/min for an hour (i.e., 0.075 mg/kg/min ketamine and 0.225 mg/kg/min propofol).

Once fully sedated, 4 mL of blood for biochemical and 1 mL for hematological assays were obtained from the cephalic vein in plain and Ethylenediaminetetraacetic acid (EDTA) tubes, respectively. Blood was drawn at time 0 (before induction) as well as 30 and 60 minutes after induction (during maintenance). Hematology was performed by an automatic hematology analyzer (Maccura F810®, China). Serum for biochemical analysis was extracted and stored at -20 ^{0}C. Analysis was performed by spectrometry using Erba Mannheim® (Erba Corporate Services, United Kingdom) kits and a UV spectrophotometer (Biochrom® Libra S50PC, United Kingdom).

Hematological assessment included absolute White Blood Cell count (WBC); relative Lymphocyte, Monocyte and Neutrophil count; together with the total Red Blood Cell (RBC), Hematocrit (HCT) and Hemoglobin concentration (Hb). Biochemical parameters studied were Alanine aminotransferase (ALT), Aspartate transaminase (AST), Blood Urea Nitrogen (BUN) and Creatinine.

Data Analysis

Data analysis was done using Microsoft Excel 15 (Microsoft Corporation, USA) and the Statistical Product and Service Solutions (SPSS) version 20 (IBM Corporation, USA) for descriptive statistics and comparison of means. Linear plots were used to express the changes in parameters throughout the maintenance period. Means and standard deviations of numerical values were determined and analysis of variance (ANOVA) together with a Post Hoc Tukey's test were used to compare variations between protocols. A dependent Student's t-test was used to compare variations within each treatment protocol from the established baseline (pre-induction) values. Data were expressed in terms of means ± standard deviation, and the statistical level of significance was set at $p \leq 0.05$.

RESULTS

Comparisons of means among the five protocols did not reveal any statistically significant differences in the lymphocyte, neutrophil, monocyte, RBC, HCT, Hb, BUN, and creatinine (figure 1,2 and 3). Within protocols, pre-induction and post-induction values for lymphocyte, monocyte, and HCT did not differ significantly as well.

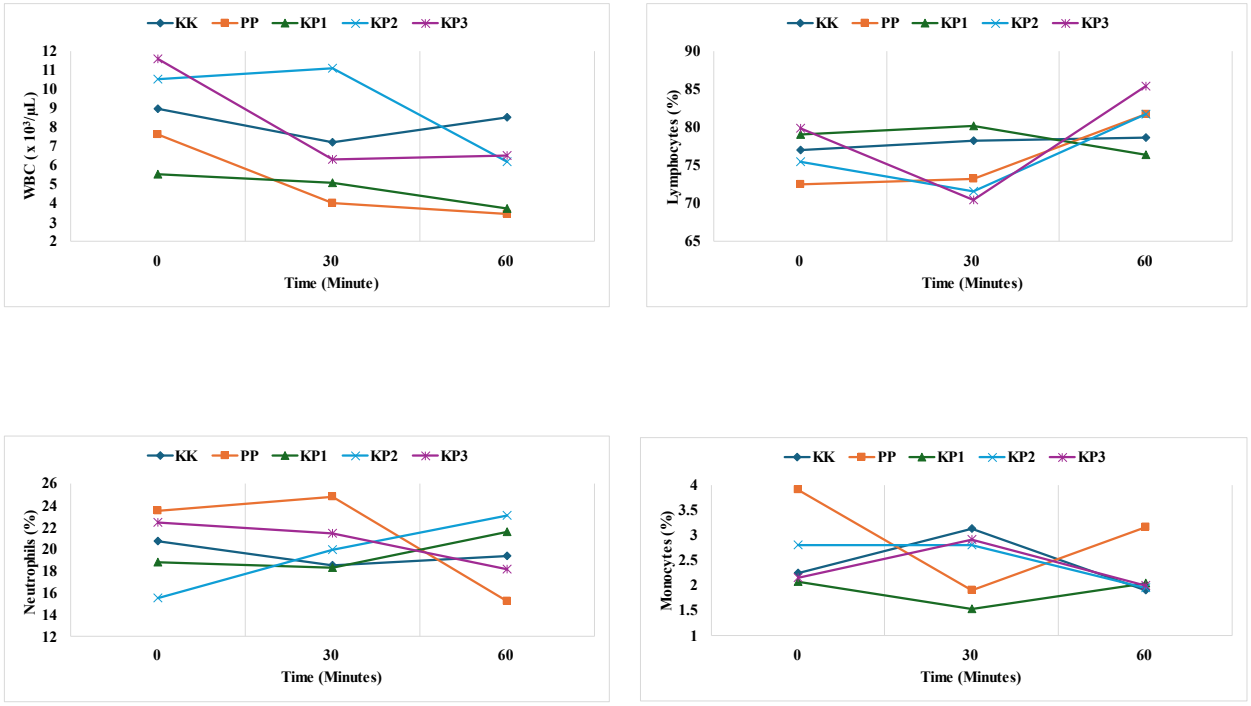


Figure 1: Mean absolute WBC; differential lymphocyte, neutrophil and monocyte count following CRI of Ketamine (KK), Propofol (PP); ketofol at 1:1 (KP1), ketofol at 1:2 (KP2) and Ketofol at 1:3 (KP3) ratios in mixed breed dogs

Significant differences among the five protocols were noted in WBC (*p=0.002*), ALT (*p=0.047*), and AST (*p=0.012*). KP2 had the highest mean WBC count (9.27 ± 2.67 x 10^3/µL), while KP1 had the lowest (4.78 ± 0.92 x 10^3/µL). KP2 also recorded the highest mean ALT (10.74 ± 0.24 U/L) and AST (12.22 ± 3.1 U/L) concentrations.

Within protocols, there was a significant decrease in WBC count in KP3 at the 30th (*p=0.009*) and 60th (*p=0.033*) minutes. A statistically significant reduction in Hb was also noted in the KP3 group at the 60th minute (*p=0.049*), while a significant increase in neutrophil count was observed in KP2 post-induction (*p=0.041*). Creatinine concentration also significantly increased from the 30th to 60th minute (*p<0.001*).

https://doi.org/10.4314/tvj.v41i2.14

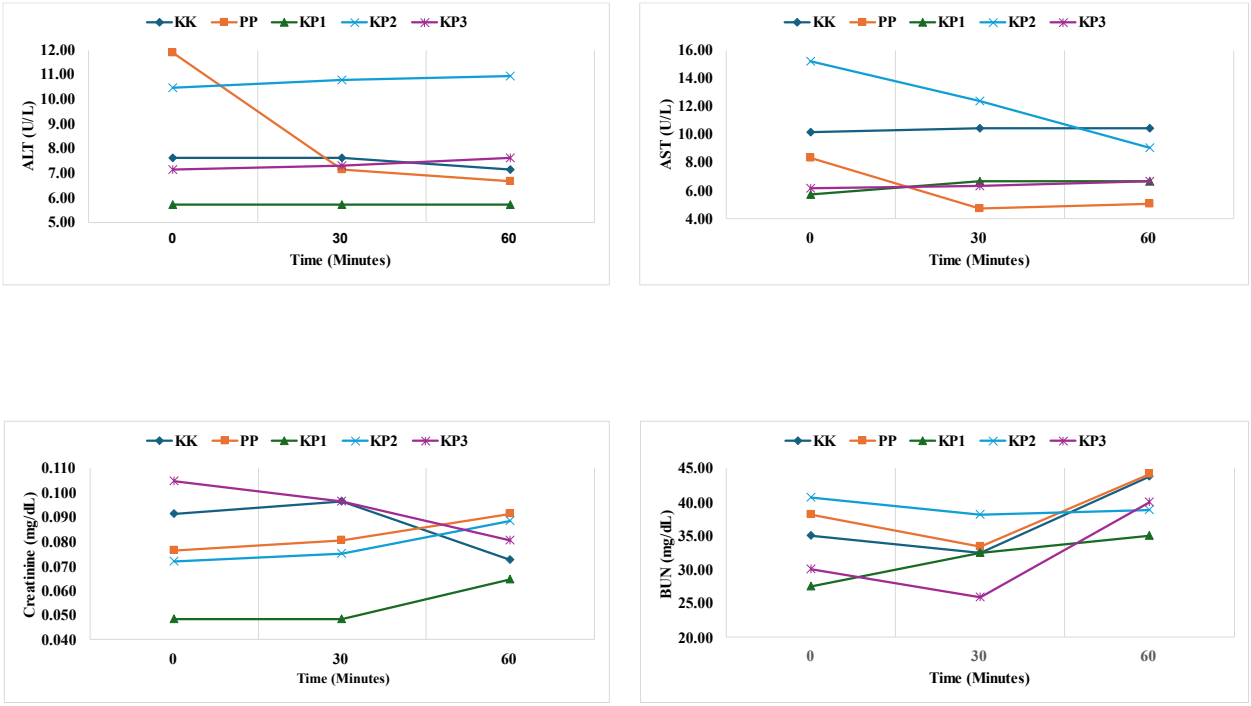


Figure 2: Mean ALT, AST, Creatinine and BUN concentration following CRI of Ketamine (KK), Propofol (PP); ketofol at 1:1 (KP1), ketofol at 1:2 (KP2) and Ketofol at 1:3 (KP3) ratios in mixed breed dogs

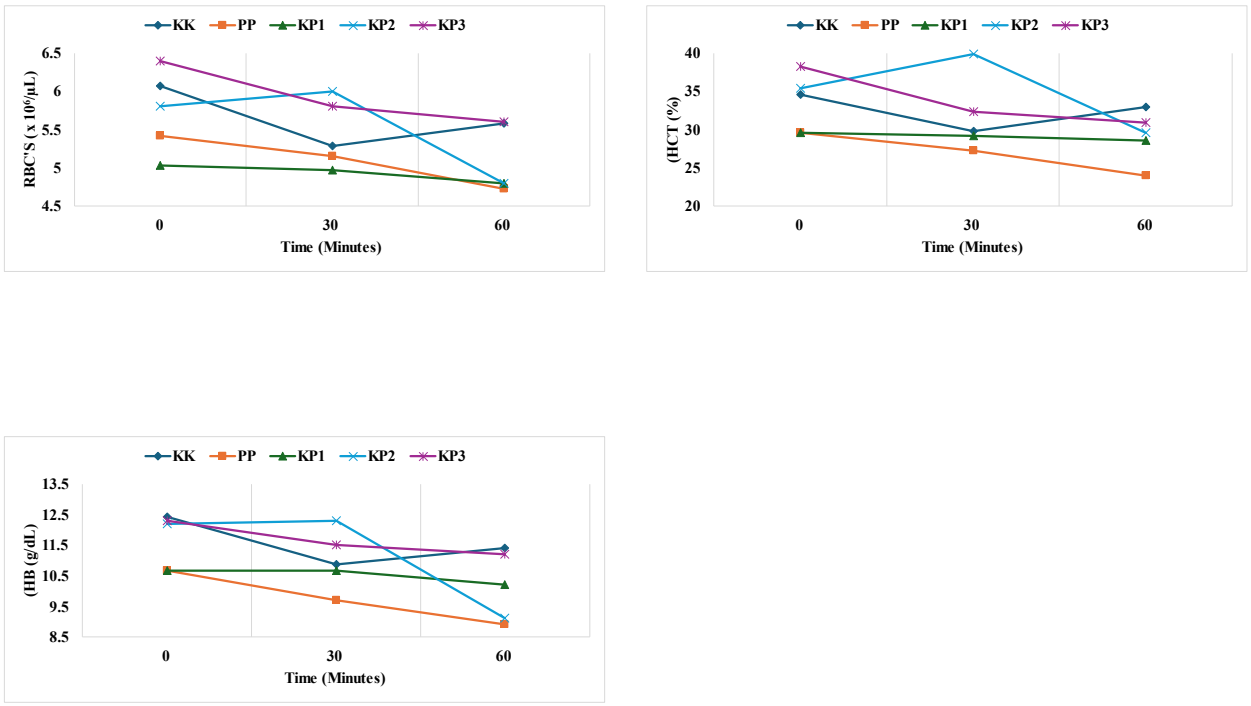


Figure 3: Mean RBC, HCT and Hb following CRI of Ketamine (KK), Propofol (PP); ketofol at 1:1 (KP1), ketofol at 1:2 (KP2) and Ketofol at 1:3 (KP3) ratios in mixed breed dogs

All other changes within groups were not statistically significant, although there was a general increase in BUN and a decrease in WBC, monocytes, RBC, HCT, Hb, and AST in all groups post-induction.

DISCUSSION

This study has demonstrated a decrease in WBC that is consistent with previous studies that used either ketamine, propofol, or their combinations in dogs. Costa *et al.* (2013) and Tomihari *et al.* (2015) reported a decrease in WBC count during maintenance in animals anaesthetized with propofol. Saikia *et al.* (2022) reported a non-significant decrease in WBC count at the 60th minute in dogs anaesthetized with ketamine, propofol and ketofol (1:1). Similarly, Camkerten *et al*. (2013) described a non-significant reduction in the WBC count during anaesthesia in Bozova greyhounds anaesthetized with a xylazine-ketamine combination. Reduction in WBC has mainly been associated with the anaesthetic plane and side effects of the drugs. The anaesthetic plane reduces stress response of the animal, while catecholamines and glucocorticoids that are released during anaesthesia may also suppress the immune system (Elenkov and Chrousos, 2002) via indirect mechanisms operating through the central nervous system (Molina, 2006). Costa *et al.* (2013), however suggested that the decrease in WBC counts may not be a result of propofol, since the drug enhances antioxidant efficiency and promotes lower release of catecholamines. Immunosuppression has been linked to hypotension in rats (Hirsh *et al*., 2002), one of the effects of propofol. These effects may result in a decrease in lymphocyte production and function.

In this study, there was a significant increase in the relative neutrophil count in the KP2 group, and a non-significant increase in KP1 as well. Saikia *et al.* (2022) reported non-significant neutrophilia up until the 60th minute when ketamine, propofol, and ketofol (1:1) were used in dogs. Non-significant neutrophilia was also reported by Jena *et al.* (2014) in dogs anaesthetized with propofol. Similar trends were noted by Sankar *et al.* (2011), who recorded neutrophilia in both ketamine- or propofol-anaesthetized dogs; Venugopa *et al.* (2002), when ketamine was used; and Kumar *et al*. (2014), when ketofol was used. Neutrophilia has been associated with anaesthetic stress coupled sometimes with painful surgeries (Sankar *et al*., 2011; Saikia *et al.*, 2022). Stress stimulates the adrenal cortex, resulting in the production of glucocorticoids. The glucocorticoids act on the circulating neutrophils, resulting in transient neutrophilia. Anaesthetic stress and changes in white blood cell proportions may have resulted in the relative increase in neutrophils observed in KP1 and KP2 groups in this study, since the animals were not subjected to any pain while being monitored.

The mean relative monocyte count in all protocols at the 60th minute was less than the pre-induction values, suggesting a decrease in the overall monocyte count. The decrease was, however, not statistically significant. Saikia *et al.* (2022) also reported non-significant decreases in the monocyte count at the 15th and 30th minutes in ketamine, propofol, and ketofol (1:1) groups. Sankar *et al.* (2011), however, reported a significant decrease in monocytes in both ketamine- and propofol-anaesthetized dogs. Similar trends were also reported by Jena *et al.* (2014), Venugopa *et al*. (2002), and Kumar *et al.* (2014) when propofol, ketamine, and ketofol were used, respectively.

All protocols used in this study had varying levels of decrease in the RBC count at the 60th minute in comparison to pre-induction values.

A study by Camkerten *et al*. (2013) reported a non-significant decrease in the RBC count in Bozova greyhounds anaesthetized with a xylazine-ketamine combination. There was also an overall reduction in the HCT in all groups in the study when pre-induction values were compared to values at the 60th minute. Camkerten *et al*. (2013) also reported non-significant reductions in the HCT in Bozova greyhounds anaesthetized with a xylazine-ketamine combination. The hemoglobin concentration decreased in all groups at the 60th minute. The decrease was statistically significant in KP3 but not significant in PP, KK, KP1, and KP2 groups. Costa *et al.* (2013) reported non-significant differences in Hb in dogs anaesthetized with propofol, while Saikia *et al.* (2022) reported a significant decrease in Hb in all dogs treated with either ketamine, propofol, or their combination (ketofol at 1:1) at the 30th and 60th minutes. Similar results were also reported by Sankar *et al.* (2011), who recorded a significant decrease in Hb in both ketamine- and propofol-anaesthetized dogs.

Reasons for the decrease in RBC, HCT, and Hb in this study are unclear; however, it has been associated with splenic pooling of erythrocytes because of a decrease in sympathetic stimulation. This is a common side effect of most of the anaesthetic agents (Kinjavdekar *et al.,* 2010; Singh *et al.,* 2013; Saikia *et al.,* 2022). Propofol has, however, been reported not to cause significant splenic enlargement (O'brien *et al.,* 2004; Wilson *et al.,* 2004); thus, the decrease, especially in propofol use, may result from sequestration of red blood cells into non-splenic sites (Costa *et al.,* 2013). The decline has also been associated with fluid shifts between body compartments to maintain normal cardiac output (Wagner *et al.,* 1991), vasodilation (Pagel *et al.,* 1998), or hemodilution because of fluid therapy (Rehm *et al*., 2000; Kinjavdekar *et al.,* 2010; Singh *et al.,* 2013).

Alanine aminotransferase (ALT) is a specific enzyme produced by the liver (Nagode *et al*., 1996). The trend of changes in the ALT level observed in this study was not uniform among the five treatment groups. KK and PP had an overall decrease in the concentration of ALT, while KP2 and KP3 had non-significant increases at the 60th minute. Saikia *et al.* (2022) described a significant increase in ALT towards the 60th minute in dogs that received ketamine, propofol and their combination at equal ratio (1:1). Similar findings were also reported by Celestine *et al.* (2014) in West African dwarf goats. Camkerten *et al.* (2013), however, reported a non-significant decline in the ALT level in Bozova greyhounds that were anaesthetized with a xylazine-ketamine combination. Increases in ALT have been associated with a combined effect of hypotension and hypoxemia, which may result in the release of the enzyme from the liver (Celestine *et al.*, 2014). The increase in ALT may also be an indication of hepatocellular damage. In this study, only two groups (KP2 and KP3) had increases in the ALT levels; one maintained a constant concentration (KP1), while the remaining two (KK and PP) had a decrease in the concentration of the enzyme. The reason for the trend is unclear.

In this study, the KK group had a gradual increase in AST during the maintenance period up to the 60th minute. An increase in AST following ketamine use has also been reported by Saikia *et al.* (2022), who suggested that the relatively higher increase in AST in the ketamine group when compared to propofol and ketofol groups may be indicative of the less adverse effects of the latter on body tissues when compared with ketamine. The AST level serves as an indication of the status of muscle and liver injury (McGill, 2016). The increase in AST in this study, however, is of less clinical significance when compared to ALT.

Creatinine levels may be used as an indication of renal function through estimation of Glomerular Filtration Rate (GFR) (Hokamp and Nabity, 2016). There was a general combined increase in the mean creatinine

concentration in all groups during maintenance. In particular, the PP, KP2, and KP3 groups had increases throughout the maintenance period, while KK had an initial increase in the first 30 minutes followed by a decrease towards the 60th minute. Saikia *et al.* (2022) also recorded a significant increase in creatinine in the ketamine, propofol, and ketofol groups. The increase in creatinine levels has been linked to reduced renal blood flow due to the inhibitory effects of the drugs, but also to the production of the substance due to muscle damage and degeneration of amino acids (Restitutti *et al.*, 2012; Singh *et al*., 2013). It is not clear if similar mechanisms may explain changes observed in our study. Follow-up tissue and organ function assessment would have provided further insight

Serum creatinine combined with Blood Urea Nitrogen (BUN) concentrations may routinely be used to further explain the status of GFR, hence renal function (De Loor *et al.*, 2013). The overall increase in Blood Urea Nitrogen (BUN) in KK, PP, KP1, and KP3 groups observed in this study was also reported by Saikia *et al.* (2022). Manat & Kelawala (2004) also reported an increase in BUN after propofol use. The increase in BUN has been associated with temporary inhibition of renal blood flow by the anaesthetic drugs. The inhibition may have resulted in a decrease in the glomerular filtration rate, thus an increase in the level of circulating BUN (Gonz'alez *et al*., 2003; Saikia *et al.*, 2022). BUN can also be altered by dehydration and, to a greater extent, by either protein catabolism, synthesis, or both processes (Fox, 1989).

Overall, the protocols appeared to have minimal effects on hematological and biochemical indices studied. This is because there were non-significant differences in most of the parameters when pre-induction values were compared to those at the end of the one-hour infusion. However, due to the varying levels of decrease in red blood cell counts, hematocrit, and hemoglobin concentration noted in all the protocols, it is imperative to diligently monitor animals under anaesthesia but also ensure a patent airway when TIVA is to be used in mixed-breed dogs. It is also important to be cautious about the use of propofol in immunosuppressed dogs due to the suppression of white blood cell production observed. Some of the limitations of the current study include the use of a small sample size of dogs in ASA I or II, which may not be a full representation of animals requiring anesthetic intervention. The use of xylazine and atropine in the protocol may have influenced some observed changes; this was controlled by administering the drugs to all the animals. The outcomes may also not apply to animals subjected to longer durations under anaesthesia. A follow-up assessment of the status of tissues and organs was not performed, but it would have provided a better understanding of some of the changes observed.

ACKNOWLEDGEMENTS

We extend our utmost and sincere gratitude to Sokoine University of Agriculture (SUA) through Sokoine University of Agriculture's Higher Education for Economic Transformation (SUA-HEET) project for providing financial support to conduct this study.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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