Effects of total intravenous anesthesia using ketamine and propofol combinations on physiological and anesthetic parameters in xylazine-premedicated mixed-breed dogs

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Abstract The physiological effects of total intravenous anesthesia (TIVA) using three different combinations of ketamine and propofol (“ketofol”) at 1:1 (KP1), 1:2 (KP2) and 1:3 (KP3) in nine xylazine-premedicated adult mixed-breed dogs were assessed. The dogs weighing 13.6 ± 2.7 kg were divided into three treatment groups in a repeated crossover experiment. A single bolus injection was used for induction, whereas constant rate infusion (CRI) was utilized for maintenance of anesthesia. All combinations lowered the respiration rates with no variations among the protocols (p=0.197). Within protocols, the rate was significantly lower than the preinduction values at the 30th (p=0.019) and 40th (p=0.041) minutes in KP1 and at the 30th minute (p=0.038) in KP2. The pulse rate was within the normal physiological range, with no differences between protocols (p=0.062); however, within protocols, the rate was significantly lower after the 30th minute in KP1 and after the 15th minute in KP2 postinduction. The temperature was within the normal physiological range but relatively higher in KP1 (p<0.001), with no differences among the protocols during maintenance (p=0.925). The oxygen saturation was generally low and did not differ significantly among the groups (p=0.542). The induction and recovery qualities were rapid and smooth, respectively, in all treatments. In all the treatments, apneustic breathing was the most common side effect. In conclusion, all ketofol ratios can be used in mixed-breed dogs; however, the 1:3 (KP3) combination had relatively more stable physiological parameters, fewer side effects and quicker recovery.

Keywords: Ketofol, CRI, Burette

1. Introduction

Total intravenous anesthesia (TIVA) is the practice of administering anesthetic drugs for induction and maintenance strictly through the intravenous route without the need for any inhalation agents (Campbell et al 2001). The development of intravenous anesthetic agents with rapid induction, distribution, and clearance, such as propofol, has contributed to increased interest in TIVA among veterinary practitioners and further necessitated by the high cost and unavailability of sophisticated anesthetic equipment, along with a lack of required expertise, especially in the field (Saikia et al 2022).

TIVA often involves anesthetic induction by administering a bolus dose aimed at achieving the required blood concentration of the anesthetic drug, followed by maintenance through target-controlled infusion (TCI), intermittent bolus infusion or constant rate infusion (CRI) (Waelbers et al 2009). TCI uses a computer-controlled infusion pump that delivers a predetermined drug concentration based on the patient’s weight or age to achieve the required plasma or brain drug concentration. In intermittent bolus infusion, an estimated amount of the drug is administered within a short time.

Constant rate infusion delivers a constant amount of short-acting anesthetic drug per unit time, thus producing a more stable plane of anesthesia over extended periods to cover the amount of time required for the animal to be under general anesthesia. The common delivery method for CRIs is calibrated syringe pumps; however, intravenous infusion sets such as burettes may also be used (Rastabi et al 2021). Compared with intermittent bolus infusion, this technique has also been reported to result in less cardiopulmonary depression and other negative effects and is thus relatively safer for animals (Njoku 2015).

One of the commonly used drugs in TIVA is propofol (Ambros et al 2008). It is an alkyl phenol compound with rapid and smooth induction, short duration of action, noncumulative properties, good muscle relaxation and quick, smooth, and excitement-free recovery of animals (Hall et al 2001). Propofol has, however, been associated with dose-dependent respiratory depression (Aguir et al 2001), apnea, little to no analgesia, decreased cardiac output and reduced arterial blood
pressure (Smith et al. 1993), but the effects are well tolerated by healthy dogs and cats (Berry 2015). It has also shown compatibility with drugs such as xylazine and ketamine; hence, the drugs may be used to potentiate its action and counterbalance its side effects (Hall et al. 2001; Celestine et al. 2014).

Ketamine is a dissociative anesthetic agent that stimulates the sympathetic nervous system, thus assisting in counterbalancing the depressant effects of drugs such as xylazine or propofol when used simultaneously and stabilizing hemodynamics during anesthesia (Lerche et al. 2000; Waelbers et al. 2009). It also assists in producing analgesia through the inhibition of N-methyl-D-aspartate (NMDA) receptors in the thalamic and limbic systems (Hall et al. 2001) and through its effect on opioids, mainly μ (μ) receptors. In contrast, anesthetic dosages of ketamine have been associated with muscle stiffness, convulsions, high incidences of agitation and violent recoveries (Kennedy and Smith 2015; Lin et al. 2015); thus, the use of drugs such as xylazine during premedication or propofol during induction and maintenance may improve its effect (Hall et al. 2001).

When ketamine is combined with propofol, the hypnosis and cardiovascular depression caused by propofol counterbalance the psychomimetic and cardiostimulatory effects of ketamine (Inteligano et al. 2008).

A 1:1 ketamine:propofol combination ratio has been used but is associated with aggravated respiratory depression in dogs (Mair et al. 2009; Kennedy and Smith 2015; Rastabi et al. 2021). Few studies have also been undertaken in mixed breed dogs to determine their physiological responses to anesthetic agents. Studies on some officially recognized breeds have revealed breed-specific metabolic and physiological peculiarities that could affect the pharmacokinetics and pharmacodynamics of drugs in different dog breeds (Fleischer et al. 2008).

This study was conducted to determine the effects of different combinations of ketamine and propofol on physiological parameters in mixed breed dogs.

2. Materials and Methods

Nine clinically healthy mixed breed dogs of either sex with an average weight of 13.6 ± 2.7 kg aged between 2-4 years were randomly purchased from wards within Morogoro region in Tanzania. The health status of the animals was determined by physical examination and assessment of the blood profile, i.e., complete blood count (CBC) and serum biochemistry. The exclusion criteria were pregnancy/lactation, aggressiveness, any form of therapy and signs/symptoms of disease. The dogs were kept for at least two (2) weeks in separate cages for acclimatization, health checkup, deworming and vaccination prior to commencement of the study. They were fed the same diet throughout the study period. The animals were fasted for 12 hours but provided with water ad libitum until 3 hours before anesthetic induction. Premedication was achieved through administering 0.04 mg/kg atropine (Swiss Parenterals Ltd®, India) and 2mg/kg Xylazine (Interchemie®, Netherlands) via the semitendinosus muscle. Fully sedated animals were initially placed on sternal recumbency for catheterization and anesthetic induction through the cephalic vein, then later on lateral recumbency for maintenance of anesthesia. The animals received 3 different treatments to cover ketofol at 1:1 (KP1), 1:2 (KP2) and 1:3 (KP3). Each treatment was repeated twice, with a one-week period between treatments using the same protocol and a two-week washout period when the animals were subjected to a different protocol.

Anesthetic induction was achieved through slow intravenous administration of a single bolus and maintenance through constant rate infusion for one hour using a burette set (Neomedic®, United Kingdom) with a drop factor of 60. 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 achieved through 0.3 mg/kg/min (0.15 mg/kg/min propofol and 0.15 mg/kg/min ketamine). In KP2, induction was achieved by 4 mg/kg ketofol (1.3 mg of ketamine + 2.6 mg of propofol per kg body weight), and maintenance was achieved through 0.3 mg/kg/min (0.1 mg/kg/min ketamine and 0.2 mg/kg/min propofol). In KP3, induction was achieved by 4 mg/kg ketofol (1 mg of ketamine + 3 mg of propofol per kg body weight), and maintenance was achieved through 0.3 mg/kg/min (0.075 mg/kg/min ketamine and 0.225 mg/kg/min propofol).

The ketofol mixture was reconstituted to a total volume of 60 ml, and the mixture was not used for more than one hour.

The parameters recorded were rectal temperature, respiration rate, pulse rate and oxygen saturation. Rectal temperature was measured using a digital thermometer, and the respiration rate was determined via auscultation using a stethoscope and observation of chest movements. The pulse rate and oxygen saturation were obtained from a pulse oximeter (Choice MMed®, China) attached to the animal’s tongue throughout the procedure. Parameters were recorded before induction (0 min) and at 5, 10, 15, 20, 30, 40, 50 and 60 minutes postinduction while the animals were under maintenance of anesthesia. The infusion was discontinued at the 60th minute postinduction.

Other parameters assessed included the quality and period of induction, anesthetic depth and recovery in addition to side effects, if any. Assessment of the quality of induction, anesthetic depth and recovery was adopted from Mair et al. (2009), Kennedy and Smith (2015) and Rastabi et al. (2021) with minor changes.

Analysis was performed using Microsoft Excel 15 (Microsoft Corporation, USA) and Statistical Product and Service Solutions (SPSS) version 20 (IBM Corporation, USA) for descriptive statistics and comparisons of means. Linear plots were
used to express changes in parameters throughout the maintenance period. The means and standard deviations of the numerical values were determined, and analysis of variance (ANOVA) together with 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 (preinduction) values. The data are expressed as the means ± standard deviations, and the statistical level of significance was set at p<0.05.

3. Results

The overall quality of induction and recovery was good, with an induction time of approximately 20 seconds in all groups. The average recovery times were 50 ± 26, 55 ± 38 and 40 ± 29 minutes in the KP1, KP2 and KP3 groups, respectively. The side effects observed in different dogs in KP1 were apneustic breathing, urination, tachypnea, tachycardia and vomiting. KP2 had tachypnea and irregular breathing in 1 dog and apneustic breathing in 3 dogs. In KP3, there was urination in three dogs during recovery and apneustic breathing in one dog.

No significant differences in the respiration rate (Figure 1) were observed among the three protocols (p=0.197). However, KP3 was more stable (10 ± 1.1 cycles/minute) than KP1 (10 ± 3.6 cycles/minute) and KP2 (10 ± 1.6 cycles/minute). Comparisons within protocols revealed significant reductions in the respiration rates at the 30th (p=0.019) and 40th (p=0.041) minutes in KP1 and at the 30th (p=0.038) minute in KP2. No statistically significant differences were observed in KP3.

A comparison of the pulse rates among the protocols (Figure 2) did not reveal any significant differences (p=0.062). However, the pulse rate in KP3 (104 ± 5.3 beats/minute) appeared relatively more stable than that in KP1 (122 ± 15.2 beats/minute) and KP2 (111 ± 27.9 beats/minute). Within protocols, statistically significant reductions were noted at the 30th, 40th and 50th minutes in KP1 as well as at the 15th, 20th, 30th, 40th and 50th minutes in KP2. No statistically significant differences were observed in KP3.

The temperature remained within the normal physiological range (Figure 3), but there were significant differences among the treatment protocols (p<0.001). KP1 was more stable (39.1 ± 0.05 °C) than KP2 (38.8 ± 0.0.16 °C) and KP3 (38.7 ± 0.08 °C). There were no significant differences within protocols during maintenance (p=0.925).

The oxygen saturation in all groups remained relatively low compared to standard physiological values (Figure 4), and there were no significant differences among the groups (p=0.542). However, KP3 had slightly higher and more stable values (89 ± 2.2%) than KP1 (86.1 ± 6.1%) and KP2 (87 ± 3.2%). Within-group comparisons did not reveal any statistically significant differences.
4. Discussion

4.1. Anesthetic drug considerations and effects

The ketofol induction dose was selected following previous studies by Kennedy and Smith (2015) and Rastabi et al. (2021). The maintenance dose also followed the results of Kennedy and Smith (2015). Generally, combining ketamine and propofol reduces the dose required for the induction and maintenance of anesthesia. A similar observation was made by Kennedy and Smith (2015) in female beagles and Mannarino et al. (2012) in mixed breed dogs. Further reductions in anesthetic requirements can also be achieved using premedication because of the anesthetic-sparing effects of some premedication drugs, such as alpha-2-adrenergic agonists (Dewangan et al. 2010; Kinjavdekar et al. 2010). In this study, xylazine was used as a premedication agent.

The induction quality and time required for a smooth transition to unconsciousness observed in this study coincide with other reports (Berry 2015). The slightly longer recovery periods observed when a higher ketamine dose was used may be a result of its slow clearance from body compartments due to redistribution. The postinduction apnea observed during this study is consistent with the findings of studies by Lerche et al. (2000) and Mair et al. (2009). The incidence of postinduction apnea is dependent upon the dosage and rate of drug administration (Mair et al. 2009), since a slightly lower incidence (18%) was reported after the slow administration of propofol by Aguiar et al. (2001). A slow titration of up to 90 seconds has been suggested by Berry (2015) to reduce the incidence of postinduction apnea.

The vomiting observed in some animals in this study could be associated with the use of the alpha-2-adrenoceptor agonist xylazine, as it is reported to stimulate the chemoreceptor trigger zone of the brain in cats, resulting in nausea and thus vomiting (Colby et al. 1981).

4.2. Monitoring of vital signs

4.2.1. Respiration and oxygen saturation
The respiratory depressant effect observed in this study and reported in other studies (Kennedy and Smith 2015; Rastabi et al 2021) could be due to the ability of ketamine and propofol to decrease the response to carbon dioxide and arterial hypoxemia (Rastabi et al 2021) but could also be a classical complication of xylazine (Clarke and Trim 2013). Combining the three drugs xylazine, propofol, and ketamine may also exacerbate respiratory depression. The initial reduction in the rate in the early stages of the maintenance period, as observed in the KP1 and KP2 groups, may have been an effect of a single bolus induction dose that contributed to high plasma concentrations of anesthetic drugs and, in some cases, excessive depth of anesthesia.

The low oxygen saturation observed in all protocols may have resulted from the low supply of oxygen due to reduced respiration and apneustic breathing patterns. It could also be a consequence of vasoconstriction because of xylazine and ketamine use (Kuusela et al 2000).

4.2.2. Pulse rate

The significant increase in heart rate during ketofol anesthesia in comparison to that of propofol alone (Kennedy and Smith 2015) has been mainly attributed to the effect of ketamine in the mixture, as ketamine is reported to increase heart rate and systemic arterial pressure (Haskins 1985). The reduction in pulse rate observed in the KP3 group might have been due to the lower ketamine dose used in the combination and to the effects of xylazine administered during premedication. Xylazine causes physiological sinoatrial and atrioventricular heart block, thus resulting in bradycardia (Hall et al 2001).

4.2.3. Temperature

The reduction in temperature observed during this study, similar to that reported by Adetunji et al. (2002) and Seliska et al. (2007), could be attributable to central nervous system depression and a reduction in muscle activity caused by anesthetic agents (Seliska et al 2007) and a decrease in environmental temperature resulting in a reduction in an animal’s body temperature (Adetunji et al 2002).

4.2.4. Limitations

Some of the limitations of this study include the fact that only 9 animals were used and that the maintenance period lasted for only 60 minutes. More animals and extended monitoring periods would have provided further insight into the general effects of the drug combinations. Furthermore, the mean arterial blood pressure and carbon dioxide concentration were not determined and could have provided additional understanding of the effects on the cardiopulmonary system.

5. Conclusions and Recommendations

Generally, the 1:1, 1:2 and 1:3 ketamine:propofol combination ratios can be used in mixed breed dogs premedicated with xylazine and atropine in procedures expected to last for approximately one hour. However, due to low respiration rates and low oxygen saturation, it is imperative to perform diligent monitoring, supplement the animals with oxygen, and ensure a patent airway. Under the conditions of this study, the 1:3 Ketamine:Propofol combination (KP3) appeared to result in relatively more stable and predictable physiological effects with fewer side effects than the 1:1 and 1:2 Ketamine:Propofol ratios. Further studies with increased sample sizes and monitored parameters together with postanaesthetic follow-up could provide more insight into the short- and long-term effects of drug combinations in mixed breed dogs.

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Ethical consideration

This study was approved by the Research Ethical Committee of Sokoine University of Agriculture, Morogoro, Tanzania.

Conflict of interest

Authors do not have any conflict of interest.

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