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Effects of maintenance of propofol-ketamine anesthesia with repeat bolus and constant rate infusion of propofol on physiological, biochemical, anesthetic and analgesic indices in dogs

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A B S T R A C T

The research work was aimed at investigating physiological, biochemical, analgesic and anesthetic indices of dogs anesthetized with propofol-ketamine and maintained with repeat bolus and constant infusions of propofol. Eight dogs, assigned to two groups (n=4), were used in this study. All dogs were pre-medicated with atropine (at 0.03 mg/kg bwt) and xylazine (at 2 mg/kg bwt). Anesthesia was induced by a concurrent administration of propofol (at 4 mg/kg bwt) and ketamine (at 2.5 mg/kg bwt). Maintenance of anesthesia in Group 1 was done with a repeat bolus of propofol (at 2 mg/kg bwt), while in Group 2 it was done with a constant infusion of propofol (at 0.2 mg/kg bwt/min). Gastrotomy was performed in both groups, and anesthesia was maintained for 60 min. Physiological, analgesic, anesthetic parameters and plasma glucose concentration were measured. There was no significant (P>0.05) difference found in the analgesia and pedal reflex scores, durations of analgesia and recumbency, recovery time and standing time between the groups. The heart rate, respiratory rate and rectal temperature reduced significantly (P<0.05) from the baseline values. The heart and respiratory rates were significantly (P<0.05) lowered in Group 1 than in Group 2. Blood glucose was significantly (P<0.05) elevated at recovery from anesthesia in both groups. However, the value did not differ significantly (P>0.05) between the groups. In conclusion, both maintenance protocols are suitable for dogs, although the repeat bolus technique produces marked cardiopulmonary depression.

Keywords

Analgesia, Anesthesia, Ketamine, Physiological effect, Propofol, Stress

ARTICLE HISTORY

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INTRODUCTION

Propofol, 2, 6-diisopropyl phenol, is an anesthetic agent belonging to the alkyl phenol group (Hall et al., 2001). It has a rapid onset of action, poor analgesic and good muscle relaxation properties, short duration of action, and is associated with a complete and excitement-free recovery from anesthesia (Hall et al., 2001). Because of its short duration of action after a single injection, it may not be considered as an anesthetic of choice for procedures requiring prolonged anesthesia. However, if propofol is the preferred induction agent for such surgical procedures, it is imperative that anesthesia can be maintained with either propofol (Gupta et al., 2007; Martin-Mateos et al., 2013, Caines et al. 2014; Chui et al., 2014; Dahi et al., 2015), or other intravenous agents (Andaluz et al., 2003; Andaluz et al., 2005; Andreoni and Hughes, 2009; Meierhenrich et al., 2010; Junior et al., 2013).

The limitation of using propofol associated with the short duration of action has been largely addressed with the introduction of the repeat bolus and the constant infusion of propofol as maintenance protocols for anesthesia. The use of the repeat bolus technique is an older technique which has been largely replaced by the constant infusion of propofol, as revealed by the trend in recent researches (Seliskar et al., 2007; Wiese et al., 2010; Chui et al., 2014; Dahi et al., 2015). The reason for this shift has not been sufficiently documented.

Martin-Mateos et al. (2013) compared the total maintenance dose of propofol using the repeat bolus

and constant rate infusion techniques in women undergoing vaginal termination of pregnancy, and reported that a total maintenance dose given in the constant infusion group was significantly greater than the bolus technique. They also reported that both the time for the patient to stop counting at induction and the time to the start of surgery were longer in the infusion group. From this finding, one would expect that the repeat bolus should be a preferred maintenance method to the constant infusion method. However, the recent trend points to the contrary. It is important, therefore that a reasons, if any, be documented for reference purposes.

The objective of this study was to establishing the differences in stress response, analgesic and anesthetic indices in dogs maintained with either repeat bolus or constant infusion of propofol.

MATERIALS AND METHODS

The study was approved by, and followed the research guidelines of the Research Ethics Committee of the Department of Veterinary Surgery and Threiogenology, Micheal Okpara University of Agriculture, Umudike.

Eight adult mongrel dogs (4 males and 4 females) were used for the study. The dogs were assigned to two groups of four animals per group (two males and two females. The dogs weighed 10.4±2.7 kg. They were obtained from the local markets in Umuahia and housed one dog per cage. They were fed cereal based food with meat and fish every morning. Water was provided *ad libitum.* The dogs were allowed two weeks to acclimatize to local conditions. During this period, blood and fecal samples were collected from the dogs and checked for endo- and hemo-parasites. Only dogs adjudged to be healthy based on clinical and laboratory examinations were included in this study.

Food and water were withdrawn from the dogs at least twelve hours and six hours respectively before premedication (Adetunji et al., 2002). Prior to medication, the animals were weighed. The rectal temperature, heart, pulse and respiratory rates were measured using a clinical thermometer, stethoscope, digital palpation of the femoral artery, and visual observation of excursions of the thorax during respiration respectively. Blood was collected from the cephalic vein for both blood sugar analysis (using an ACU-CHEK ACTIVE (Roche, Germany) and total and differential leukocyte count. Venepuncture of the cephalic vein was performed using an intravenous cannula.

All dogs were premedicated with atropine sulphate (at 0.03 mg/kg bwt), and xylazine (at 2 mg/kg bwt). Anesthesia was induced with a concurrent administration of propofol and ketamine at 4 mg/kg bwt and 2.5 mg/kg bwt, respectively. Maintenance of anesthesia lasted for 60 min in all groups.

A 0.03% propofol for intravenous infusion was prepared by dispensing 15 mL of propofol (1%) in 485 mL of 0.9% NaCl. The preparation was contained in a 500ml saline infusion bag (Adetunji et al., 2002).

Anesthesia was maintained in Group 1 with repeat bolus infusion (RBI) of propofol at 2 mg/kg bwt every 10 min. A constant infusion of normal saline was commenced as soon as anesthesia was induced, and stopped after 60 min. In Group 2, anesthesia was maintained with constant rate infusion (CRI) of propofol at 0.2 mg/kg bwt/min, which commenced immediately after induction of anesthesia. The dogs in both groups were intubated 1-3 min after induction of anesthesia and allowed to breathe atmospheric air.

The skin on the ventral abdomen caudal to the level of the xyphoid was prepared aseptically for gastrotomy. Following patient preparation and anesthesia, a ventral midline skin incision approximately 8 cm in length was made on the linea alba commencing just caudal to the xyphoid. The subcutaneous tissue, linea alba and peritoneum were incised along the same line. The stomach was exteriorized and packed off with sterile gauze. An incision was then made on the parietal surface of the stomach into the gastric mucosa. The gastric incision was closed using chromic catgut, 2/0, with single layer Lambert suture pattern. The peritoneum with the muscles and subcutaneous tissues were closed with size 2/0 chromic catgut in simple continuous suture pattern. The skin was closed using size 2/0 monofilament silk in a horizontal mattress suture pattern (Venugopalan, 2000).

Following gastrotomy, the dogs were hospitalized and observed for one week. The surgical wounds were dressed daily. Procaine penicillin (at 15000 IU/kg bwt) and streptomycin (at 25 mg/kg bwt) were administered intramuscularly on recovery from anesthesia, for four consecutive days.

The following parameters were measured:

1. The duration of analgesia (mins): measured as the time interval between the reduction in toe web reflex and the time of resumption of the reflex.
2. The analgesia score. The score was calibrated as follows:

a. Movement on pin prick around the ventral abdomen 0
b. Movement on incision of skin and subcutaneous incision 1
c. Movement on incision of muscles 2
d. Movement on incision of peritoneum 3
e. Movement on incision of the stomach 4
f. No movement during the entire procedure 5

3. Pedal reflex score: The reflex was assessed and scored as follows:
   a. Limb withdrawal at the lock of the first ratchet of a hemostat clamped on the toe web 3
   b. Limb withdrawal at the lock of the second ratchet 2
   c. Limb withdrawal at the lock of the third ratchet 1
   d. No limb withdrawal at the lock of third ratchet 0

   The reflex was assessed 10, 30 and 60 min after the induction of anesthesia.
4. Duration of recumbency (min): time, which is the interval between xylazine-induced recumbency and the dogs' assumption of sternal posture (Adetunji et al., 2002)
5. Standing time, which is the time interval (in seconds) between assumption of sternal posture and the dogs' ability to stand (Adetunji et al., 2002).
6. Recovery time (min) measured from the time of the last administration of propofol and the dog's ability to stand (Adetunji et al., 2002).
7. The heart rate (beats per min) was measured using a stethoscope placed on the left chest wall over the apex of the heart, prior to premedication, at induction of anesthesia, and every 10 min during anesthesia.
8. The respiratory rate (breaths per min) measured by visual observation of thoracic movements. The respiratory rates were measured and recorded at the same times as the heart rate.
9. The rectal temperature (^{0}C) measured using a digital clinical thermometer inserted into the rectum and anchored to the side of the rectum till a beep sound is heard. The temperature was measured and recorded at the same times as the heart rate.
10. The blood glucose level (mg/dL) was measured using a glucometer (Acu-Check Active, Roche, Germany).

RESULTS

The results of the experiment showed that the dogs had sufficient analgesia to withstand the surgery. The mean analgesia score was greater than 4.5 in both groups (**Figure 1**), and the score did not differ significantly (P>0.05) between the groups. This similarity in the analgesia score was also observed in the mean pedal reflex score, where the score in both groups reduced over time throughout the procedure. The pedal reflexes in both groups reduced significantly (P<0.05) between the 10th and the 30th and 60th min post induction of anesthesia. There was no significant (P>0.05) difference in the analgesia scores and pedal reflex scores between the groups at the times of assessment (**Figure 2**).

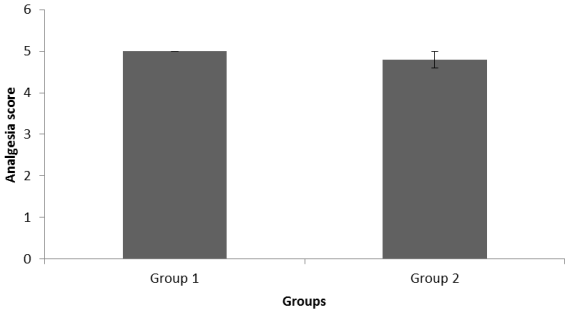

Figure 1. Mean analgesia score. No significant (P>0.05) difference between the groups.

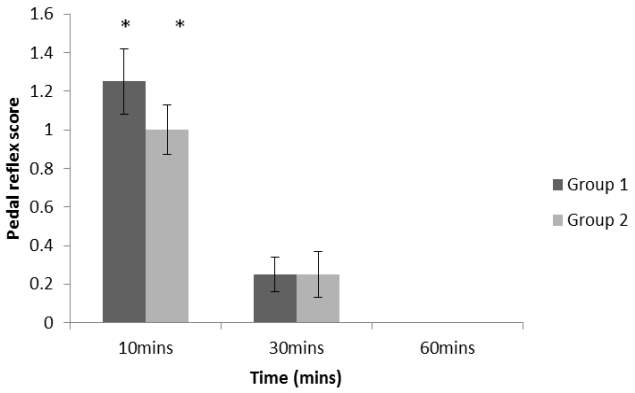

Figure 2: Pedal reflex score. *Indicates significant (P<0.05) difference in pedal reflex score at the times of evaluation

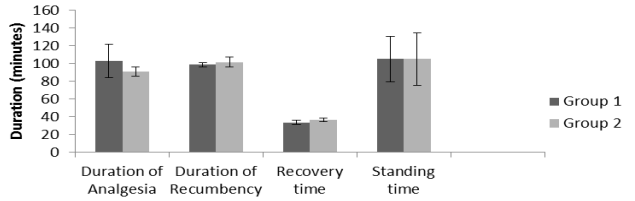

Figure 3: Duration of analgesia, duration of recumbency, standing time and recovery time. No significant (P<0.05) difference in duration of analgesia, duration of recumbency, recovery time and standing time between the groups.

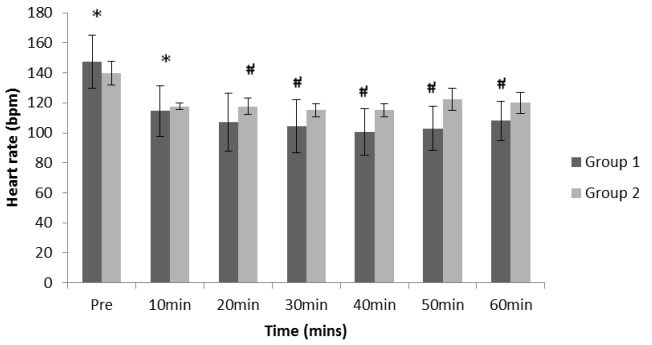

Figure 4: Heart rate. #Indicates a significant (P<0.05) difference in heart rate between Group 1 and Group 2; *Indicates a significant (P<0.05) difference between the pre-anesthetic heart rate and those measured at other times during the procedure.

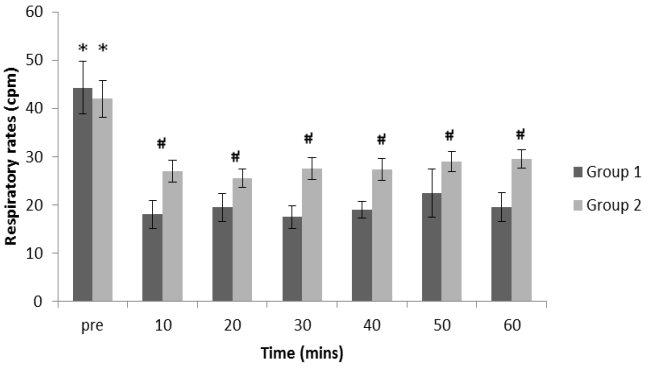

Figure 5: Respiratory rate. #Indicates a significant (P<0.05) difference in respiratory rate between Group 1 and Group 2; *Indicates a significant (P<0.05) difference between the pre-anesthetic respiratory rate and those measured at other times during the procedure.

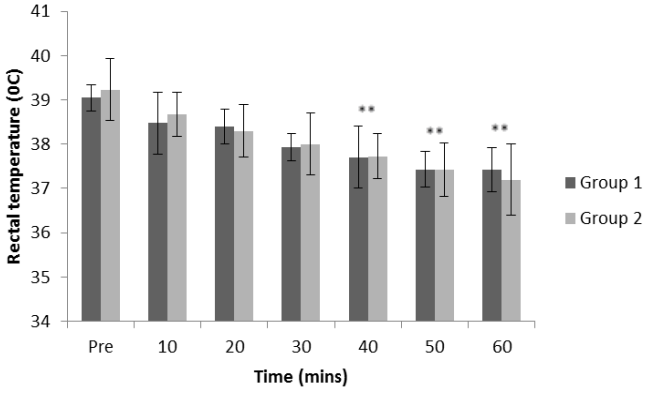

Figure 6: Rectal temperature. *Indicates a significant (P<0.05) difference in the between the pre-anesthetic rectal temperature and those measured at other times during the procedure.

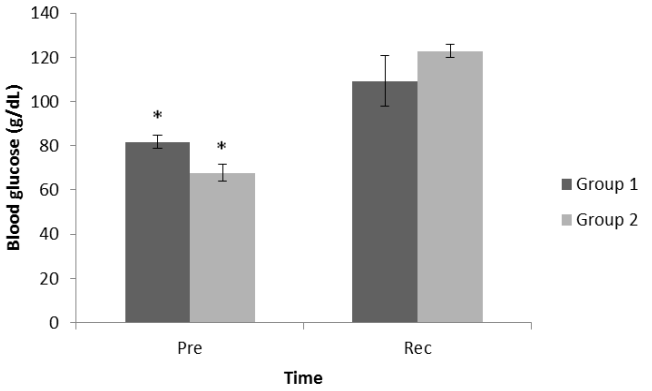

Figure 7: Blood glucose. *Indicates a significant (P<0.05) difference between the pre-anesthetic blood glucose and that measured at recovery.

The indices of anesthesia, namely the duration of analgesia, duration of recumbency, standing time and recovery time did not differ significantly (P>0.05) between the groups (**Figure 3**).

The heart and respiratory rates of dogs in both groups reduced significantly (P<0.05) from the 10th to the 60th min when compared to the pre-induction values (**Figure 4** and **5** respectively). Also, from the 20th min post induction, the heart rates of dogs in **Group 1** were significantly (P<0.05) lower than those of dogs in **Group 2**. Similarly, the respiratory rates of the dogs in **Group 1** were significantly (P<0.05) lower than those of dogs in Group 2 from the 10th to the 60th min post induction.

The rectal temperature reduced progressively throughout the procedure in both groups. This decline from the pre-anesthetic value became significant (P<0.05) from the 40th min in both groups. There was no significant (P>0.05) difference in the rectal temperature between the groups at the times when the temperature was measured (**Figure 6**).

The recovery from anesthesia in both groups was associated with a significant (P<0.05) increase in blood glucose relative to the baseline value. There was however no significant (P>0.05) difference in the blood glucose between the groups.

DISCUSSION

The results of this study showed that the indices of analgesia measured, namely the analgesia score and the pedal reflex score, did not differ significantly (P<0.05) between the groups. In both groups, equal

doses of xylazine and ketamine were administered. Xylazine is an α_2-adrenoceptor agonist, which has been reported to have good analgesic properties (Hall et al., 2001). Xylazine's analgesic effect is thought to be as a result of the stimulation of the alpha adrenoceptors at the spinal cord and brain, thereby inhibiting the release of neurotransmitters, norepinephrine and substance P (Saha et al., 2005; Kolahian, 2014). Ketamine, on the other hand, is thought to produce analgesia by inhibiting the N-methyl, D-aspartate receptors in the thalamic and limbic systems (Hall et al., 2001). Low doses of ketamine have been used in veterinary practice to produce analgesia in anesthetized dogs (Slingsby and Waterman-Pearson, 2000).

Researches in analgesia have shown that the use of a combination of analgesics which have different mechanisms of action is highly recommended (Omamegbe and Ukweni, 2010; Ukwueze et al., 2014). This is because the combination requires the use of lower doses of the individual agents to produce sufficient analgesia, thereby reducing the possibility of over dosage. This explains the sufficient analgesia observed in both groups in this study.

Generally, the mean heart rate of dogs in this study reduced significantly (P<0.05) from the preanesthetic value. Xylazine, one of the drugs used in this study, causes hypertension, which leads to a physiological sino-atrial and atrioventricular heart block, and consequently, bradycardia (Hall et al., 2001). On the other hand, atropine and ketamine both stimulate the cardiovascular system, leading to tachycardia (Clarke and Trim, 2014). While ketamine produces a sympathetic stimulation (Seliskar et al., 2007), atropine stimulates the heart by inhibiting cholinesterase release. The stimulatory effect of ketamine on the heart has been reported to be masked by the concomitant use of other agents, such as α_2-adrenergic receptor agonists (Hopster et al., 2014). Thus, the inclusion of these cardiac stimulants to the protocol may not have stimulated the heart sufficiently to produce a heart rate that is up to the baseline value after the xylazine-induced bradycardia. Ringer et al. (2012) reported that boluses of α_2-adrenoceptor agonists caused bradycardia and fall in cardiac output unlike a constant infusion of the class of drugs. Another study by Madhavi et al. (2012) which studied the changes in pulse rate of renal failure human patients that were given atracurium in intermittent or bolus infusions, reported a significant reduction in pulse rate in patients that were treated with the repeat boluses. Similarly, intermittent boluses of propofol caused a significantly lower heart rate than those of dogs whose anesthesia was maintained by the constant infusion technique. The significant (P<0.05) reduction in the heart rates of dogs in Group 1 from the baseline may also be as a result of the time at which the heart rate was monitored. For animals whose anesthesia were maintained on the repeat boluses of propofol, the heart rates were monitored shortly after the administration of the maintenance doses of propofol. At this time, the plasma concentration of propofol was at its peak, and its effect was maximal.

The respiratory rate reduced significantly (P<0.05) from the baseline in both groups from the time of anesthesia induction to the time of recovery. This observation is in line with previous reports by Jia et al. (2015). Respiratory depression has been reported as a classical complication of xylazine, (Clarke and Trim, 2014), propofol (Wiese et al., 2010) and ketamine (Clarke and Trim, 2014), all of which were used in this study. As was observed for heart rate, the respiratory rate of dogs whose anesthesia was maintained by the repeat bolus method was observed to be significantly (P<0.05) lower than those that were maintained with the constant rate infusion method. This respiratory rate of dogs in the repeat bolus group was monitored shortly after the administration of the maintenance dose, at which time the concentration and effect of propofol in the blood was maximal.

The progressive reduction in rectal temperature of anesthetized animals as observed in this study is in line with the observations of Adetunji et al. (2002) and Seliska et al. (2007) in dogs. A similar event has been reported in birds (Machin and Caulkett, 2000; Rembert et al., 2001; Langlois et al., 2003; Muller et al., 2011). Reduction in rectal temperature during surgery is usually as a result of the physiological effects of the anesthetic agents used. These agents cause central nervous system depression and reduction in muscle activity (Seliska et al., 2007). Hypothermis has also been mentioned as a factor (Andreoni and Hughes, 2009). Also, poor physical status of the patient, large surface area of incisions, deep anesthesia, long surgical procedures, infusion of cold fluids intravenously, and a low environmental temperature (Adetunji et al., 2002) have been incriminated. In this study, a wide area of the skin from the xypoid to the umbilicus was clipped. This wide area that was clipped may have contributed to the hypothermia. Another factor that may contribute to hypothermia during anesthesia and surgery include the temperature of the surface on which the animal was placed during the procedure.

Changes in plasma glucose concentration has been demoonstrated as an effective tool in determining stress response during surgery (Omamegbe and Ukweni, 2010; Udegbunam, et al., 2012; Njoku et al., 2015). Pain mediators are thought to be released as a result of acute pain caused by damage to superficial nerve endings during tissue trauma (Singh, 2003). These mediators stimulate the autonomic and central nervous systems, leading to the release of hormones, such as adrenaline, noradrenaline, cortisol and glucagon. The actions of these stress hormones lead to the delay in metabolism and utilization of glucose, gluconeogenesis, lipolysis and insulin resistance, all culminating in the elevation of plasma glucose concentration (Singh, 2003). The results of the present study shows that plasma glucose concentration was significantly (P<0.05) increased at the time of recovery when compared to the pre-surgical value. This suggests that the drugs used in this study (atropine, xylazine, ketamine and propofol) did not obliterate the response of the dogs to pain, thus, the significantly (P<0.05) increased plasma glucose. In a recent study that compared the plasma glucose concentration of goats castrated under local lignocaine infiltration with those castrated under epidural lignocaine, Njoku et al. (2015) reported that a significant increase in plasma glucose concentration was observed in the local ifiltration group, while the epidural group did not show a significant increase in the plasma glucose concentration. This demonstrates that the routes of administration of the anesthetic or analgesic influences the stress response with regards to glucose concentration. Again, Udegbunam et al. (2012) reported a dose-dependent stress response to piroxicam in rabbits. The results of the present study indicate that the difference in the methods of maintenance of anesthesia did not alter stress response significantly.

Following premedication with phenothiazines or α_2-adrenoceptor agonists, a complete recovery from propofol anesthesia after a single injection of 1% propofol (at 6 mg/kg bwt) is expected to occur in about 20 min (Hall et al., 2001). In the present study, recovery from anesthesia occurred in 33.8±2.14 min and 36.5±1.94 min in Group 1 and 2, respectively. These values were higher than the average time recorded by Hall et al. (2001). Recovery time from propofol anesthesia has been reported to be dependent on the rate of propofol infusion and the duration of maintenance of anesthesia (Seliskar et al., 2007). Post-anesthetic sleep has also been reported to occur occasionally in dogs following propofol anesthesia, and this phase is most times not distinguishable from the recovery phase of anesthesia (Clarke and Trim, 2014). In the present study, the high values for the recovery time is also thought to be as a result of the long duration of maintenance of anesthesia (60 min), and possibly a post-anesthetic sleep. Muller et al. (2011) observed an intermittent awakening from anesthesia when propofol boluses are used to maintain anesthesia in swans. In their study, however, the boluses were administered as needed, while in the present work, the boluses were given at pre-determined time intervals. The indices of anesthesia (duration of recumbency, standing time and recovery time) did not differ significantly between the groups. This suggests that the pharmacokinetics of propofol in dogs is similar when propofol is administered intermittently and when it is administered as a constant infusion. It may be deduced that the for the repeat bolus group, plasma concentration of propofol was above the minimum plasma concentration required for anesthesia in dogs. This is thought to simulate steady plasma concentration of propofol as produced in the constant infusion group.

CONCLUSION

The use of both repeat bolus and constant rate infusion of propofol for maintenance of anesthesia in dog premedicated with atropine sulphate, xylazine and ketamine did not show any difference in the duration of anesthesia, standing time, duration of recumbency, analgesia score, blood glucose concentration and rectal temperature. However, repeat boluses of propofol significantly reduced the heart and respiratory rates. The findings of this study therefore suggest that the use of constant rate infusion of propofol has the tendency of causing less cardiopulmonary depression, and other deleterious effects arising from it, and is therefore safer than the repeat bolus infusion. This justifies the shift in preference from repeat bolus to constant infusion technique.

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