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Research Article

Comparative Evaluation of the Anaesthetic Indices of Propofol in Varying Combinations With Diclofenac and Tramadol in Dogs

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ABSTRACT

This study compared the anaesthetic indices and vital parameters of dogs given propofol with varying analgesic combinations. Nine dogs assigned into three groups were administered Propofol 8mg (IV) combined with Diclofenac 2mg/kg IM -DP group; Tramadol 5mg/kg IM- TP group and Diclofenac 2mg/kg + Tramadol 5mg/kg IM-DTP group. Heart and respiratory rates, temperature and selected anaesthetic indices were determined over a 40-minute period. Onset and duration of analgesia were statistically significant (p<0.05) among groups. Onset of analgesia was D-T-P < T-P < D-P. Duration of analgesia was longest in the T-P group and shortest in D-P group. The duration of anaesthesia was statistically significant (p<0.05) among groups, however onset of drug action was not (p>0.05). In conclusion, the three analgesic-propofol combinations produced anaesthesia of moderate duration. However, the T-P and D-T-P had better outcome based on their faster onset and longer duration of analgesia.

Keywords: *Anaesthesia, propofol, diclofenac, tramadol, vital parameters, dogs*

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INTRODUCTION

Anaesthesia is an indispensable prerequisite for most surgical interventions in animals (Muir *et al.*, 2013). However, most of the available anaesthetic drugs lack vital components such as analgesia and muscle relaxation (Barry, 2015). Propofol is a hypnotic drug with actions characterized by speedy onset, satisfactory sedation, good haemodynamic stability and rapid unexcited recovery (Weaver and Raptopaulos, 1990; Muir *et al*., 2007 Barry, 2015). It is commonly used as an anaesthetic induction and maintenance agent when administered as repeated bolus injections or as a continuous rate infusion (Muir *et al*., 2007). Propofol is rapidly metabolized by cats and dogs, with clearance approximately 10 times faster than that of thiopental sodium (Shafer, 1993). It however, lacks analgesic properties, and this limits its usefulness for painful surgical procedures (Muir 2007). The need for drug combinations for complementary effects have therefore been suggested (Sinyl, 2003). Drugs with desirable qualities, which lack essential analgesic or muscle relaxing properties may be combined with alpha-2 adrenoceptor agonists (xylazine, medetomidine, dexmedetomidine) or benzodiazepines (diazepam, midazolam, zolazepam) to produce ideal general anaesthesia (Sinyl, 2003; Raposo, 2009). Propofol combination with available analgesics: opioid, Non-Steroidal Anti-inflammatory Drugs (NSAID), and their combinations is a current subject of research (Iannarone *et al*., 1997; Sinyl, 2003; Bayan and Konwar, 2014). Also, combination of more than one class of analgesic drug for pain is a newer trend in pain management (Jin and Chung, 2001; Leigh, 2008). Employing multimodal analgesic combination with propofol may produce a superior analgesic effect for use in short duration painful procedures than combination with a single analgesic drug.

The aim of this study, therefore, was to compare the anaesthetic effects of propofol in combination with diclofenac and tramadol together and singly with a goal of providing alternative anaesthetic protocol for short painful surgical procedures in dogs.

MATERIALS AND METHODS

Experimental Animals

Nine clinically healthy local dogs (five females and four males) between the ages of 5 and 8 months, with an average weight± SEM of 7.3±2.2 kg were used for this study. The experimental dogs were housed in cages and fed twice daily with home diet. Water was provided ad libitum. The dogs were allowed a two-week acclimatization period during which they were conditioned for daily human contact such as; playing, petting and grooming. Prior to commencement of the experiments, the dogs were adjudged healthy following results of complete physical examination and blood sample analysis.

Drugs

The drugs used for this study were:

a) Propofol, (PropoFlo® Zoetis, New Jersey, USA) supplied as a 10mg/ml solution for intravenous injection in a 20-ml ampoule.
b) Tramadol Hydrochloride (Tramaden®, Laborate pharmaceutical, India) supplied as a 50mg/ml solution for intramuscular or intravenous injection in a 2-ml ampoule.
c) Diclofenac sodium (Tromax® Medline, India) was supplied as a 50mg /ml aqueous solution for intramuscular or intravenous injection in a 2ml ampoule.

Study design: The nine dogs were randomly assigned to three treatment groups of 3 dogs each. The first experiment involved the intramuscular administration of diclofenac (premedication) followed 5 minutes later by intravenous administration of propofol (D-P group). The second and third groups of experiments were similarly carried out but with premedication with tramadol (T-P group) and mixture of diclofenac and tramadol (D-T-P group). In the course of each experiment, heart rate (HR), pulse rate (PR), respiratory rate (RR) and rectal temperature (RT) of the anaesthetized dogs were obtained. An initial set of physiological parameters (baseline values) were taken before premedication, immediately after premedication and after onset of drug action following anaesthetic induction with propofol and then subsequently at 5 minutes intervals for a period of 40 minutes. Selected anaesthetic indices were also recorded.

Experimental procedure: The experimental dogs were fasted overnight but allowed free access to water until 2 hours before drug administration. Vital parameters including heart rate, respiratory rate and rectal temperature were measured before premedication and ringer's lactate at a rate of 5ml per kg/hour was administered to maintain a patent venous access for intravenous drug administration. In the first group (D-P), 2mg/kg diclofenac was injected intramuscularly as premedicant. Vital parameters were checked and recorded. Five minutes later, propofol at 8mg/kg was slowly administered intravenously into the cephalic vein through the preplaced intravenous catheter as a single bolus. The second and third groups were similarly treated but with 5mg/kg tramadol for premedication (TP group) and a mixture of 2mg/kg diclofenac and 5mg/kg tramadol (DTP group). Following the loss of the righting and palpebral reflexes, the dogs were placed on lateral recumbency. The dogs were left un-intubated and allowed to breathe in room air. The digit pinch withdrawal reflex on both hind limbs was used to test for analgesia at 2 minutes interval with the aid of a haemostatic forceps engaged at the first ratchet. Lack of withdrawal of either hind limb following forceps application was interpreted as analgesia.

Calculated anaesthetic indices*:* The anaesthetic indices were calculated as follows:

a) *Onset of drug action* (OD): Time interval (in min) between the injection of propofol and the loss of righting and palpebral reflexes by the dog.
b) *Onset of analgesia* (OA): Time interval (in min) between the injection of propofol and the loss of pedal withdrawal reflex in either hind limbs by the dog.
c) *Duration of analgesia* (DA): Time interval (in min) between the loss and return of pedal withdrawal reflex in either of the hind limbs by the dog.
d) *Duration of anaesthesia*: time interval (in min) between the loss of righting and palpebral reflexes and assumption of sternal posture by the dog.
e) *Recovery time* (RRT): Time interval (in min) between the assumption of sternal and standing postures by the dog.

Measured physiological variables

In the course of the trials, heart rates (HR), respiratory rates (RR) and rectal temperature (RT) were determined before drug administration (base line values), immediately after premedication and onset of anaesthesia following induction with propofol, and thereafter, at 5 minutes intervals over a 40-minute period of anaesthesia. Heart rate (in beats/min) was determined with the aid of a precordial stethoscope placed over the left second and fifth intercostal spaces, respiratory rate (in breaths /min) was determined by observation of the dog's thoracic excursions. The rectal temperature (in ^{o}C) was determined using a digital clinical thermometer.

Data analysis: Data was organized and analyzed using Graph Pad Prism version 6. All data were expressed as mean ± standard error of mean (SEM). Analysis of Variance (ANOVA) with repeated measures was used to detect the significant differences of mean values of physiological parameters and anaesthetic indices at 95% confidence interval.

RESULTS

Anaesthetic indices

There was no significant difference ($p>0.05$) in the onsets of drug action for all the three drug combinations. The D-P had the longest duration of anaesthesia (32.5±0.2min) followed by T-P (30.9± 0.3min) while the D-T-P had the shortest duration of anaesthesia (29.3±0.2min). Onset of analgesia was significantly longer ($p<0.05$) with D-P than both T-P and D-T-P combinations. The duration of analgesia was longest with the T-P dogs (30.3±0.2min), intermediate with the D-T-P (28.6±0.1) and shortest with the D-P group (26.6±0.3min). The D-T-P recorded the longest recovery time with the D-P recording the shortest recovery time (Table 1).

Table 1:
Anaesthetic indices of nine dogs following propofol anaesthesia with various analgesic combinations

Index	Drug combination		
	D-P	T-P	D-T-P
Onset of drug action	2.6± 0.1	2.3± 0.2	2.4± 0.2
Duration of anaesthesia	32.5± 0.2	30.9± 0.3	29.3± 0.2
Onset of analgesia	13.5± 0.4*	9.5± 0.2	9.0 ± 0.2
Duration of analgesia	26.6± 0.3	30.3 ± 0.2	28.6± 0.1
Recovery time	4.1± 0.2	5.2± 0.4	6.7± 0.1

Temperature responses of dogs to the propofol analgesic combinations: The temperature of the experimental dogs ranged from 38.0± 0.2 to 39.1± 0.2$_0$C (D-P); 38.6± 0.4 to 39.2±0.0 $_0$C (T-P) and 38.4±0.4 to 39.0±0.2$_0$C (D-T-P). There was a slight fall in rectal temperature after the administration of propofol for all combinations. The temperatures rose slightly after 20 minutes (Figure 1).

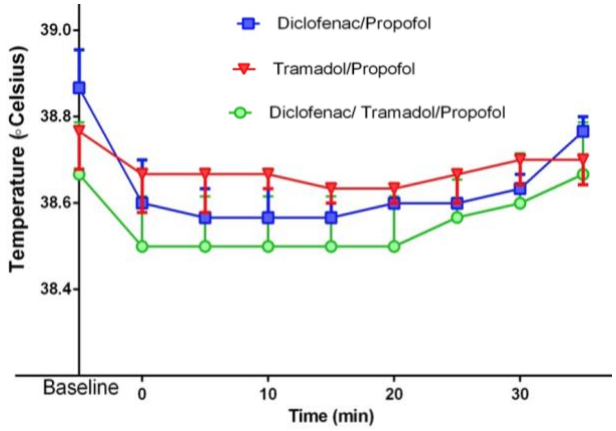

Figure 1
Rectal temperature responses of dogs to the administration of diclofenac/propofol; tramadol/propofol and diclofenac/ tramadol/propofol.

Heart rate responses of dogs to the propofol analgesic combinations: The heart rates recorded were generally irregular with no definite pattern. They ranged from 118.0±0 to 127.3±5.0 beats/minute for the D-P dogs, 114.0±0 to 123.7±2.5 beats/minute (T-P group) and 114.0±3.5 to 121.3±2.9 beats/minute (D-T-P group) (Figure 2).

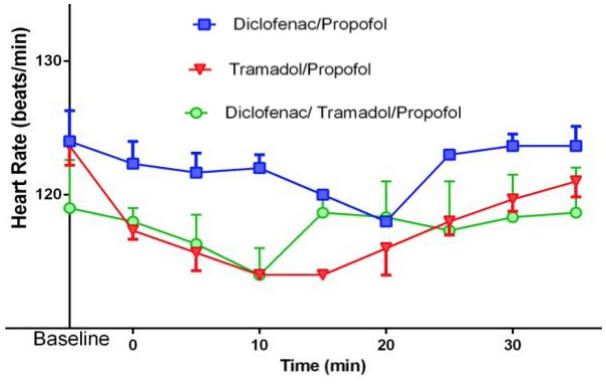

Figure 2:
Heart rate responses of dogs to the administration of diclofenac/propofol; tramadol/propofol and diclofenac/ tramadol/propofol.

Respiratory rate responses of dogs to propofol analgesic combinations: Mean respiratory rates ranged from 15.0±1.7 to 29.3±4.2 breaths/min (D-P); 12.3±0.6 to 27.0±4.6 breaths/min (T-P) and 15.3±2.9 to 34.0±7.5 breaths/min (D-T-P). There was a general decrease in respiratory rates for all three analgesic-propofol combinations from time of drug administration and for the first 20 minutes of anaesthesia. The T-P combination had lower respiratory rates compared to the others (Figure 3).

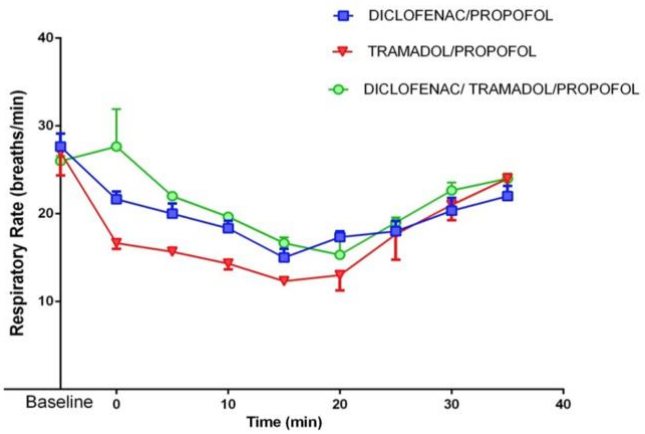

Figure 3:
Respiratory rate responses of dogs to the administration of diclofenac/propofol; tramadol/propofol and diclofenac/ tramadol/propofol.

DISCUSSION

The result of this study showed that propofol in combination with the analgesic drugs produced anaesthesia of moderate duration. The D-T-P group had the fastest onset but intermediate duration of analgesia. Conversely, the T-P group had the longest duration but intermediate onset of analgesia (Table 1). This finding of a longer duration of analgesia in the T-P than the D-T-P group but a shorter onset of analgesia is not surprising. It was expected that the D-T-P group would produce a better quality of analgesia considering the combination of two analgesic drugs. The combination of opioids with NSAIDS is frequently employed for post-operative pain management and has been shown to provide better analgesia than the single use of either analgesics (Jin and Chung, 2001).

The observed greater depth of anaesthesia with the D-P than the T-P and D-T-P groups (Table 1) is surprising because it would have been expected that the CNS depressant effects of opioids and hypnotics (Kukanich and Papich, 2004) contributed by tramadol which is a synthetic opioid (Guedes *et al.*, 2005) would produce a greater depth with the tramadol combinations (T-P and D-T-P groups) (Kukanich and Papich, 2004). Nonetheless, the longer recovery of the D-T-P and T-P groups than the D-P group could be clearly attributed to the CNS depressant effects of opioids and hypnotics (Guedes *et al.*, 2005) contributed by tramadol in these groups (Grond and Sablotzki, 2004).

The duration of anaesthesia obtained in the three groups (Table 1) is greater than the 15-20 minutes for propofol when

used alone (Reid and Nolan, 1999). There was significant difference ($p<0.0001$) in mean temperature, heart and respiratory rates in all three analgesic/ propofol combinations. However, all vital parameters were within normal ranges for dogs implying good safety with their use. The decrease in heart and respiratory rates observed in the T-P and D-T-P groups compared with baseline values may have been influenced by the combined cardio-pulmonary depressant effects of propofol and respiratory depressant effects of tramadol as observed in previous studies (Papich *et al*., 1995; Amengual *et al*., 2013). The temperatures also all fell within the normal temperature range of 37.5 to 39.2 ^{0}C for dogs (McKelvey and Hollingshead, 2000).

In conclusion, the three analgesic-propofol combinations produced anaesthesia of moderate duration. However, the T-P and D-T-P had better outcome based on their faster onset of action and longer duration of analgesia.

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