1. **INTRODUCTION**

In domestic animals, anaesthesia usually include premedication to provide tranquilization or light sedation which facilitate animal handling, securing of venous access, aseptic patient preparation, followed by anaesthetic induction and then maintenance with either inhalation or intravenous agents (Clarke, et al.,2014). It is established that anaesthetic quality of premedicant plays a vital role in the reduction of the side effect as well as volume of anaesthetic induction and maintenance agent. Phenothiazines especially Acepromazine (ACP) is a widely used anaesthetic premedicant in Veterinary Surgery with the intention to produce muscle relaxation and sedation in dogs. Despite their sedative effects, these drugs lack analgesic effects (Hall, 2001). Opoids (like Morphine, Butorphanol and Buprenorphine) are commonly used in small animal anaesthetic premedicant to provide varying level of analgesia. Butorphanol and Buprenorphine are both partial opoid agonists that are capable of producing short and long duration of analgesia respectively (Izer et al., 2014) and are thus used as small animal premedicants. Phenothiazines (example Acepromazine) are commonly referred to as tranquilizers or neurolept and they are usually combined with agents having potent sedative and analgesic property (e.g opoids) to produce a state of profound central nervous system depression and induce general anaesthesia -a concept often refer to as Neuroleptanalgesia (Poller, et al., 2013; Chang, et al., 2014). Neuroleptoanalgesia provide synergism between the two drugs (Neurolept and Opoids) leading to greater sedation and analgesia unlike when individual drug is used alone (Monteiro, 2009). Undesirable cardiopulmonary effects have been reported in dogs premedicated with Acepromazine-Buprenorphine and Acepromazine-Butorphanol with Propofol as induction and maintenance agent using Total Intravenous Anaesthesia (TIVA) (Bolaji-Alabi, Adetunji, 2018). Although Acepromazine has been associated with dose dependent cardiopulmonary effect in dogs (Popovic, et al., 1972), these may have been aggravated by continuous administration of Propofol as TIVA. This is because Propofol can also cause vasodialation leading to decreased arterial blood pressure; decreased myocardial contractility and dose-dependent respiratory depression (Clarke, 2014). There is paucity of information on the comparative effects of both neuroleptanalgesics (Acepromazine-Buprenorphine and Acepromazine-Butorphanol) in dogs anaesthetized with Propofol and maintained with Isoflurane. Thus these drugs are used without adequate information on the cardiopulmonary disturbances associated with their use as premedicants with Propofol and Isoflurane. This study was carried out to compare the cardiopulmonary and analgesic effects, to assess anaesthetic safety in dogs premedicated with either Acepromazine-Butorphanol or Acepromazine-Buprenorphine which were induced and maintained with Propofol and Isoflurane respectively.

1. **MATERIALS AND METHOD**

**2.1 Animal management**

Six apparently healthy Nigerian indigenous dogs (3 males and 3 females) weighing between 7-10kg with mean age of 2.0 ± 0.4 years were used for this prospective, cross-over blinded clinical study. The study was conducted as two trials with a ‘wash-out’ period of one week between each trial. The animals were maintained in iso-managemental conditions (for 3weeks) with enough once daily food (rice, fish) and water (ad-libitum). They were dewormed and vaccinated. They were kept off feed and water for 12 and 6 hours respectively, before commencement of the treatment. This research work was carried out at the Veterinary Teaching Hospital, College of Veterinary Medicine, Federal University of Agriculture, Abeokuta (FUNAAB.), Nigeria.

**2.2 Anaesthetic protocol**

Trial I: The dogs were premedicated with combination of 0.04mg/kg Acepromazine (Kyion prescription SCC South Africa) and 0.3mg/kg-Butorphanol (MSD Animal Health, UK) while dogs in trial II received 0.04mg/kg Acepromazine and 0.03mg/kg Buprenorphine (Dechra Ltd, UK) and volume of each drug depended on their weight.

After sedation, dog was placed on right lateral recumbency. Lactated Ringer solution was administered intravenously at a flow rate of 5mlkgh-1 via a 21guage butterfly needle in the cephalic vein. A 5-lead multi-parameter patient monitor (GB3, General Meditech. Inc. China) was connected to the dogs in right lateral recumbency. A lead each to the thoracic region at the base of the heart, right fore-limb, left fore-limb, to the right hind limb and the left hind limb respectively. The blood pressure cuff was placed over the ulnar artery, on the forearm. 30minutes after premedication, induction was achieved with intravenous administration of 4mg/kg Propofol (Propofol-lipuro 10 mg/ml, Fresius Kabi, Halfway House, South Africa), in either trials. Tracheal intubation was achieved with size 7mm ID cuff endotracheal tube (D Notec® UK) Anaesthesia was maintained with 2% Isoflurane (Baxter Healthcare Ltd UK) in 2L/minute oxygen for three hours.

**2.3 Evaluation of cardio-pulmonary parameters** The baseline values for clinical and physiological parameters were recorded before injection of the drug in each animal in each trial. Monitoring was continuous, records of the parameters monitored were taken at 15minute intervals and included respiratory, pulse and heart rates; peripheral Oxygen saturation (SpO2), rectal temperature, and non-invasive blood pressure (NIBP).

**2.4 Evaluation of anaesthetic indices**

Anaesthetic indices such as time to extubation (TE, time interval between the end of Isoflurane administration and return of voluntary swallowing), time to sternal recumbence (TSR, time interval between TE and return to sternal position) and time to stand (TS, time interval from TSR to stand up) and observable side effects were recorded.

2.5 Statistical analysis

The data obtained were expressed as means ± Standard deviation (SD). The data were subjected to variance Least Significant Difference for comparison between the trials. Also, Wilks’s Lambda Multivariate test was used to evaluate variations in parameters measured between the groups at different time intervals. Data was analysed using Graph pad prism version 5. Value of P≤ 0.05 was considered significant.

**3. RESULTS**

 **3.1 Cardio-pulmonary parameters**

The cardiopulmonary parameters measured in this study were comparable in all the groups and did not differ significantly (p>0.05). The heart rate decreased in the two trials after premedication (Figure 1). There was significant increase (p<0.05) in heart rate at 45min post premedication in Acepromazine-Buprenorphine (trial II) (127±9bpm) compared to Acepromazine-Butophanol (trial I). Trial II had a non- significant (p>0.05) decrease in heart rate at 60 minutes post premedication and the values fluctuated till 90 minute before progressively increasing beyond the baseline towards the end of the trial. Meanwhile heart rate in Trial I decreased progressively towards the end of the trial. In the Acepromazine-Buprenorphine trial, heart rate was higher when compared with trial I during anaesthesia until extubation. A progressive but non-significant (P>0.05) increase in pulse rate was observed in trial I at 15 to 45 minutes post-premedication followed by a progressive decrease in pulse rate that tended towards the base value recorded at 180 min of observation (Figure 2.). In contrast to Trial I, Trial II animals showed an initial non-significant (P>0.05) decrease in pulse rate at 30 minutes post premedication followed by significant (p<0.05) increase at 45 minutes post premedication which thereafter decreased at 60 and 75minutes and increased progressively afterwards till end of trial although not significant (P>0.05). Among the trials, a non-significant (P>0.05) variation in pulse rate at 30 minutes was observed.

A non-significant (p>0.05) increase in mean arterial pressure (MAP) recorded in both Trial I and II at 30 minutes post administration of premedicant followed by an immediate progressive decrease in MAP in both groups till 60 minutes post administration of premedicants (Figure 3). The lowest MAP was recorded at 60 minutes in Acepromazine-Butorphanol premedicated group which progressively increased afterwards tending towards the base value at 180 minute of observation. In contrast, Acepromazine-Buprenorphine premedicated dogs showed a non-significant (p>0.05) downward fluctuation in MAP from 60 minutes post premedication throughout the observation period which was below the baseline values (hypotension).

The two trials generally showed an increase in respiratory rate throughout the observation period (Table 1). Both trials I and II had a non-significant (p>0.05) increase in respiratory rate at 15 minutes post premedication. Significant increase (p<0.05) in respiration rate were observed at 90 minutes in trial I and 60 minutes in trial II post premedication which fluctuated thereafter till the end of the observation.

Initial non-significant decrease (p>0.05) in SpO2 was observed in trial I at 30 minutes post premedication followed by a rise in SpO2 to 96 % at 45 minutes post premedication which progressively fluctuated and maintained around 95-96% till the end of the trial (Figure 4). In contrast to this, trial II showed a significant increase in SpO2 up to 98% at 45minutes post premedication and progressively maintained around 98% till the end of the trial. Trial I SpO2 differed non-significantly with that of trial II but trial II had higher values of SpO2 throughout the study

There was significant decrease (p<0.05) in temperature observed at 90 minutes post premedication in both trials (Figure 5). Trial I showed a slightly higher temperature compared to trial II throughout the study period. Temperature in trial II progressively decreased throughout the study while it fluctuated progressively although not to the level of the baseline values in trial 1. There was no significant difference in the temperature of animals in both trials.

**3.2 Evaluation of Anaesthetic indices**

The observed side effects of the anesthetic agents used in the two trials were apnoea, shivering, hypothermia, coughing and rough recovery (Table 2). Coughing was noted in one dog each on Acepromazine-Butorphanol and Acepromazine-Buprenorphine after extubation, slight shivering was observed in all treated trials. The volume of Propofol used for induction differed significantly between the trials; 5.3±0.7ml and 2.7±0.4ml were administered intravenously in trial I and II respectively. A slightly higher volume of Isoflurane (3%) was required to maintain anaesthesia in trial I compared to 2% used in trial II. The degree of analgesia achieved by Acepromazine-Butorphanol was moderate (animals adopted recumbency and showed minimal responses to the environment) while that of the Acepromazine-Buprenorphine trial was mild (dogs lied down and they responded minimally to the environment). The quality of induction of anaesthesia with Propofol was satisfactory and without excitement in both groups, and there were no difficulties in endotracheal intubation. During Propofol injection and Isoflurane maintenance, palpebral reflexes were rarely seen, although the eyes were ventrally rotated. Induction and recovery were observed to be smooth for both Acepromazine-Butorphanol and Acepromazine-Buprenorphine. Recovery was smooth, quiet in the two treated trials and time to recovery was not statistically different between the protocols (Figure 6). The Acepromazine-Buprenorphine trial had significantly longer recovery from anaesthesia compared to the Acepromazine-Butorphanol. Sternal recumbency was achieved significantly faster in the control while there was no significant difference between the treated trials. Duration of analgesia was significantly longer in trial II (Acepromazine-Buprenorphine) than in trial I (Acepromazine-Butorphanol).

**4.0DISCUSSION** The goals of administration of premedicants in veterinary anaesthesia are to ease handling of the patient, abolish fear and anxiety, provide tissue analgesia, alleviate side effects of other anaesthetic drugs, and reduce effective dose of general anesthetic induction and maintenance agent, which ensure smooth and uneventful induction and recovery from anaesthesia (Hedenqvist, et al., 2013). Despite the fact that premedication provides above-mentioned benefits, patient under general anaesthesia are often monitored periodically to ensure their anaesthetic and physiological indices are within normal range and to give insight into patient condition which may require attention (Alam et al., 2014. In this study, time to extubation and time to sternal recumbency were both similar in the two trials (Ace-But and Ace-Bup). Also, long duration recumbency and smooth recovery were achieved with both anaesthetic protocols. However, Ace-But group had a shorter mean time to standing compared to Ace-Bup trial. The longer duration of anaesthesia in Ace-Bup could be because Buprenorphine has delayed onset of action (30-45minutes) and a long duration of action of about 5 hours in cats and dogs (Slingsby, 2011). Propofol at a dose of 4mg/kg body weight used in this study, Ace-But trial required lower volume for induction (2.7±0.4ml) compared to Ace-Bup trial (3.5±0.5ml). This showed that Ace-But had a better anaesthetic quality since it provided a lower volume of induction agent which is a desirable quality (Cornick, Janyce, 20015). When Propofol is used as induction agent or as total intravenous anaesthesia, it produces cardiopulmonary effects including lower mean arterial pressure, high heart rate (Sams, et al., 2008). post-induction apnoea and cyanosis (Maney et al., 2013). In contrast, inhalation anesthetic agents like Isoflurane are known to induce a dose-dependent cardiopulmonary depression. In this study, the two neuroleptoanalgesics possess beneficial effects and may be used for premedication in dogs to alleviate common complications associated with Propofol-induced and Isoflurane-maintained general anaesthesia. However, the observation of significantly higher pulse and heart rate in Ace-Bup trial may suggest that this combination should be used with caution in patients with inherent cardiogenic problems.

Hypothermia occurs when the rate of heat loss is greater than the production. As previously reported ‘Heat generation drops during anaesthesia, the thermoregulatory center of the hypothalamus is depressed, the metabolic rate drops, muscular activity is reduced and the use of cold-substances’ Haskins (2003). There was no significant difference in the hypothermia observed between the two trials. This could be due to longer duration of anaesthesia in the patients.

5. CONCLUSION In conclusion, either Butorphanol or Buprenorphine can be used in combination with Acepromazine for premedication of dogs for routine surgical procedures. However, Acepromazine-Butorphanol combination appears to be a better choice of neurolept-analgesic for premedication in Propofol-Isoflurane anaesthesized Nigerian indigenous dogs.

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