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Effects of Propofol Anaesthesia Pre-Medicated with Xylazine on Serum Biochemical Profiles and Sleep Pattern in Red Sokoto Goats

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ABSTRACT

This study was conducted with the objective to compare the sleep pattern and biochemical changes during general anesthesia at different timing interval with the baseline information using Propofol as the agent of choice and xylazine as a pre-medicant at 4 mg kg^{-1} intravenously and 0.025 mg kg^{-1} intramuscularly respectively. The onset of anaesthesia was rapid (30.1±11.3 seconds), the anaesthetic induction, surgical plane and recovery were good. There was a significant difference ($P<0.05$) between baseline and other timing intervals in the rectal temperature, respiratory rate, systolic and diastolic blood pressure, but there was no significant difference ($P>0.05$) in pulse rate. Similarly, a statistically significant difference ($P<0.05$) was observed in the serum calcium ion, magnesium ion, hydrogen bicarbonate ion, Alkaline Phosphatase (ALP), creatinine, total protein and glucose levels, but there was no significant difference ($P>0.05$) in the sodium ion, potassium ion, Alanine aminotransferase (ALT), Albumin (ALB), Aspartate aminotransferase (AST), , and Urea. It was concluded that the combination of Propofol and Xylazine at 4mgkg^{-1} and 0.25mgkg^{-1} respectively can be effectively and safely used for induction and maintenance of anaesthesia in Red Sokoto goats. It was also noted that recovery was smooth without any violence. The combination was also observed to have minimal effects on the clinico-biochemical parameters of Red Sokoto goats.

Key words: Propofol, Anaesthesia, Xylazine, Goat.

INTRODUCTION

In developing countries like Nigeria, general anaesthesia is hardly carried out on ruminants because the agents used for general anaesthesia are costly; and there is lack of technical know-how and the fear of anaesthetic risk. Due to these reasons, local anaesthesia, coupled with physical restraint, is widely used for virtually all surgical procedures in ruminants. However, this problem is limiting ruminant surgeons to conduct highly invasive procedures because of the limitation of the local or regional anaesthesia.

Propofol is a phenol derivative that lacked analgesic effect; it has a low molecular weight (178 D), it was reported to be insoluble in water but highly soluble in fat (Baggot, 1997: Adetunji *et al*., 2002). Propofol is being referred to as "milk of amnesia" because of the cream-like of the intravenous formulation (Eliano and Gravenstein, 2004; Kesel, 2013). The commonest available preparations in the market are:1% Propofol, 10% Propofol with soybean oil and 1.2% Propofol with purified egg phospholipids and 2.25% Propofol with glycerol as a tonicity adjusting agent (Clark, 1983).

Propofol is a short-acting, rapidly metabolized anaesthetic agent with very rapid recovery and virtually lack any cumulative effect on continuous infusion and does not damage the tissue when injected peri-vascularly and intra-arterially (Amarpal *et al*., 2002). The drug has high affinity for protein in vivo and is usually metabolized by the liver by conjugation. However, the rate at which the drug is cleared by the kidney exceeds the hepatic blood flow, which may imply the existence of an extra-hepatic site for its elimination (Vanlersberghe and Camu, 2000). Hence, total elimination of propofol from the body is estimated to last between 2 to 24 hours.

The practice of pre-anaesthetic medication with a sedative before induction of anaesthesia via injection is common among veterinary clinicians. The sedatives are

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traditionally used to achieve sedation pre-operatively in order to enhance the action of the anesthesia and to essentially reduce the amount of the injectable or inhalant anaesthesia to be administered for the successful induction and maintenance of general anesthesia (Kojima *et al*., 2002). Some of the sedatives routinely used in attaining sedation in small ruminants include; xylazine which is an α2 adrenoceptor agonists, phenothiazines like acepromazine, and benzodiazepines like midazolam and diazepam, as well as opioids like butorphano (Amarpal *et al*., 2002). Despite the popularity of Xylazine as a choice sedative in ruminants (Dehghani, 1991), complications like hypoxaemia following its administration in small ruminants is considered a significant drawback (Bacon *et al*., 1998). The development of profound hypoxaemia in sheep and goats following xylazine administration may be because of pulmonary oedema and the extravasation of red blood cells into the lung as has been earlier reported following administration of α2 adrenoceptor agonists such as medetomidine, romifidine, detomidine and xylazine (Celly *et al*., 1997).

MATERIALS AND METHODS

Experimental animals

Ten (n=10) clinically healthy intact goats of different sexes of age and body weight range of 15-20 kg were used for the investigation. The animals were kept in small ruminant's pen of Usmanu Danfodiyo University Veterinary Teaching Hospital, Sokoto, they were fed on wheat bran, bean husks, groundnut and bean hay with water *ad libitum*. The animals were conditioned for two weeks before the investigation, during which fecal and blood samples were collected to determine intestinal worm burden and haematological analysis respectively.

Animal preparations

Food was withheld from all the animals 12 hours prior to induction of the anaesthesia but the water was provided until about 6 hours to induction of anaesthesia. The left and right jugular groves were shaved and disinfected with Methylated spirit (Binji Global Pharmaceutical Company, Sokoto, Nigeria) and the two jugular veins were catheterized with Polyvinyl intravenous catheters for the administration of the Propofol (Diprivan®) and the collection of blood sample as described by Reid *et al*., 1993; Correia *et al*., 1996 and Adetunji *et al*., 2002.

Premedication and induction of anaesthesia

The animals were Pre-medicated with Xylazine 20® (Xylazine HCl 20mg/ml, Kepro Holland at 0.025mgkg^{-1}) and Atropine sulphate 0.6mg/ml (Laborate Pharmaceuticals India; at 0.05 mg kg^{-1}) before induction with Propofol (Pofol®) at 4 mg kg^{-1}. Propofol anaesthesia was maintained for 60 minutes by continuous infusion rate (CIR) at 0.4 mgkg^{1}min^{1} as described by Kaiser-Klingler, 2012; Ferreira *et al*., 2016.

Anaesthetic monitoring and scoring

The Quality of anaesthesia was assessed during surgical plane anaesthesia till recovery according to the standard procedure described by Lin *et al*. (1997). The numerical scoring values of 2, 1 and 0 were used to denote good, fair and poor response respectively (Table 1).

At the surgical plane anaesthesia phase, the sleep pattern was assessed by taking the heart (HR) and respiratory rates (RR) with Littman clinical stethoscope. Pulse rate (PR) and arterial blood pressure (ABP) were assessed using a digital blood pressure monitor placed at the cephalic region, and rectal temperature was also recorded using a digital thermometer. The parameters were assessed at baseline (0), 5, 15, 30, 45 and 60 minutes interval between induction and continuous Intermittent Bolus Injection periods; parameters were also recorded at 120th minutes after full recovery from the anaesthesia according to standard procedure described by Correia *et al*. (1996); Lin *et al*. (1997); Andaluz *et al*. (2003) and Andaluz *et al*. (2005).

Samples collection

Five (5) Ml of blood sample was collected with 5cc disposable syringe through the indwelling intravenous catheter in the left jugular vein before induction (at baseline), the sampling was continuous during surgical plane anaesthesia at 5, 10, 15, 30, 45 and 60 minutes between induction and continuous intermittent bolus injection periods and 1 hour after complete recovery. The samples were placed in plain sample bottles. The blood sample was centrifuged at 1000 rpm to harvest the serum for electrolytes determination (Sodium, potassium, Calcium, Magnesium and hydrogen bicarbonate ions) and enzyme assay (Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Albumin, Urea, Creatinine, and Glucose level were also determined (Aitkenhead and Smith, 1998).

Data analysis

Data obtained were recorded, tabulated and mean and standard deviation (Mean±SD) was computed. One-way analysis of variance (ANOVA) was used to compare statistical significance differences among the timing interval of the variable contained in the SPSS statistical package version 22.

RESULTS

The onset of anaesthesia was 30.1±11.3 seconds. There was extensive salivation, urination was frequent, the third eyelid was prolapsed and Intubation was feasible. There was no outward sign of excitement and the animal recovered quickly, walked with minimal ataxia and had no response to external stimuli during surgical plane anaesthesia, but there was vocalization in some cases. The quality of induction (QI) was good 2.00 (Median value), surgical plane anaesthesia quality (QA) was reasonably good 1.8 (Median value), and the quality of recovery (QR) was also good 2.00 (Median value) (Figure 1).

There was a significant decrease of rectal temperature with statistically significant differences ($P<0.05$) at 10, 15, 30, 45, 60 and 120 minutes when compared with the baseline (Table 2). There was also decrease in respiratory rates at different timing interval with the baseline, with a significant difference ($P<0.05$) was recorded at 30, 45 and 60 post administration of the Propofol when compared with the baseline (Table 2). There was no significant difference ($P>0.05$) of pulse rates between baseline and other timing interval post-Propofol administration,

Table 1: Criteria used to evaluate the quality of induction of anaesthesia and recovery in goats receiving Propofol anaesthesia as described by Lin *et al*. (1997)

	Response		
Stage	Good (2)	Fair (1)	Poor (0)
Anaesthetic Induction	Rapidly assumes sternal recumbency; no outward sign of excitement; easy tracheal intubation.	Mild signs of excitement; attempts to rise after resuming recumbency; responsive to tracheal intubation.	Obvious signs of excitement; do not become recumbent; poor muscle relaxation.
Recovery	When goat resumes sternal position; stands in a reasonable amount of time; is able to walk with minimal ataxia.	Some struggling; requires assistance to stand; hyper-responsiveness that disappears once goat is able to stand unassisted with a moderate degree of ataxia.	Unable to stand even with assistance, prolonged struggling
Anaesthesia	No response to the stimulus	Mild response to the stimulus	Very responsive to stimulation (gross purposeful movement, such as lifting head, chewing and vocalization).

Table 2: Sleep Pattern of Propofol Anaesthesia Pre and Post Induction (Mean±SD)

Parameters	Base line	Post Propofol Induction (Minutes)						
	0	5	10	15	30	45	60	120
RT (°C)	38.3±0.5^{a}	38.1±0.3^{a}	37.9±0.3^{b}	37.7±0.3^{c}	37.5±0.3^{d}	37.6±0.3^{e}	37.4±0.3^{f}	38.0±0.3^{g}
RR (C/min)	21.2 ±2.3^{a}	19.6±2.0^{a}	19.2±1.8^{a}	18.6±2.0^{a}	18.2±2.0^{b}	17.5±1.8^{c}	17.8±2.1^{d}	19.8±2.1^{a}
PR (B/min)	65.6±8.6	59.0±9.2	57.1±6.5	57.4 7.0	57.1±6.7	54.9± 5.9	61.0±6.2	60.7± 6.9
SBP(mm/Hg)	132.8±4^{a}	134.3.2±3^{a}	114.5±3.2^{b}	125.5±3^{c}	125.7±2^{d}	128.3±3^{e}	131.9±4.8^{f}	135.5±3^{a}
DBP(mm/Hg)	103.5±3^{a}	105.5±3.2^{b}	96.5±3.1^{c}	90.5±3.0^{d}	90.5±3.0^{e}	74.6±3.3^{f}	84.5±3.5^{g}	90.5±3.2^{h}

Means on the same row with different superscripts are significantly different (P<0.05) from the baseline at different timing: intervals.

Table 3: Mean serum biochemical profiles value pre and post propofol administration

Parameters	Baseline (minute)	Post Propofol Induction (Minutes)						
	0	5	10	15	30	45	60	120
Na^{+} (Mmol/l)	133.6±2.9	134.6±7.7	131.9±6.9	129.4±5.5	131.2±8.0	127.9±4.9	132.0±4.7	127.6±5.7
K^{+} (Mmol/l)	4.0±0.6	3.7±0.5	3.7±0.5	3.5±0.3	3.6±0.4	3.5±0.3	3.8±0.5	4.1±0.5
Ca^{2+}(mg/dl)	9.1±0.5^{a}	8.0±0.5^{b}	8.0±0.4^{c}	7.9±0.4^{d}	8.1±0.5^{a}	9.0±0.4^{a}	8.8±0.5^{a}	9.0±0.5^{a}
$Mg2^{+}$(mg/dl)	1.1±0.1^{a}	1.0±0.02^{b}	0.9±0.08^{c}	0.9±0.1^{a}	1.0±0.1^{a}	1.0±0.1^{a}	0.7±0.09^{d}	1.0±0.1^{e}
HCO_3^{-} (Mmol/l)	23.2±0.9^{a}	20.1±0.6^{b}	20.8±1.5^{c}	21.0±1.3^{d}	20.7±1.1^{e}	21.4±1.4^{f}	20.9±1.3^{g}	21.8±1.2^{a}
AST (µ/l)	16.6±3.1	18.8±2.8	18.9±3.1	18.9±2.9	19.1±4.1	19.2±4.1	18.8±4.0	20.0±3.9
ALT (µ/l)	129.6±22.0	120.1±19.9	122.8±20.5	125.7±21.0	123.7±18.9	123.9±20.0	124.4±19.8	126.1±26
ALP (µ/l)	310.0±47.2^{a}	345.7±30.1^{a}	356.1±44.7^{b}	412.5±32.0^{c}	425.8±41.0^{d}	448.5±41.0^{e}	454.0±40.0^{f}	431.9± 30.0^{g}
ALB (g/dl)	4.1±0.7	3.7±0.5	3.8±0.4	3.5±0.3	3.6±0.5	3.5±0.3	3.8±0.6	4.1±0.5
Creatinine (mg/dl)	1.35±0.1^{a}	1.0±0.1^{b}	1.2±0.09^{c}	1.08±0.1^{d}	1.08±0.1^{e}	1.1±0.1^{f}	1.2±0.1^{g}	1.31±0.1^{a}
Urea (mg/dl)	9.2±1.1	9.1±1.0	9.6±0.9	9.8±0.9	8.9±1.0	9.8±0.9	9.8±0.9	9.8± 1.0
Total Protein (g/dl)	6.1± 0.3^{a}	6.1±0.3^{a}	5.9±0.4^{a}	5.9±0.3^{a}	5.35±0.3^{b}	5.0±0.3^{c}	5.2±0.25^{d}	5.9±0.3^{a}
Glucose (Mmol/l)	10.1±0.9^{a}	9.7±1.0^{a}	9.7±0.8^{a}	8.5±1.3^{b}	9.6±1.2^{a}	9.5±0.9^{a}	8.8±1.0^{a}	9.1±0.9^{a}

Means on the same row with different superscripts are significantly different (P<0.05).

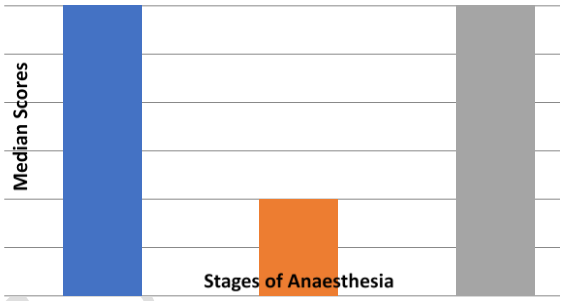

Fig. 1: Median value scores of quality of propofol anaesthesia

even though there was a slight decrease of the pulse rate at different timing interval when compared with the baseline (Table 2). There was a decrease in cephalic systolic blood pressure with statistically significant difference (P<0.05) at 10, 15, 30, 45 and 60 minutes interval when compared with the baseline (Table 2).There was also decrease of cephalic diastolic blood pressure with significant difference (P<0.05) at 5, 10, 15, 30, 45, 60 and 120 minutes compared with the baseline (Table 2).

There was decreased serum sodium and potassium ions when the baseline was compared with other timing intervals, but there were no significant differences (P>0.05) (Table 3). There was also a significant decrease of serum calcium, magnesium and bicarbonate ions with statistically significant differences (P<0.05) when the baseline was compared with other timing intervals (Table 3). Aspartate Aminotransferase (AST), Alanine Amino-transferase (ALT) and Albumin (ALB) values were decreased compared with baseline, but there was no significant difference (P>0.05) when the baseline was compared with other timing intervals (Table 3). Alkaline phosphatase (ALP) decreased significantly with statistically significant different (P<0.05) between baseline and other timing intervals (Table 3). Creatinine, total protein and glucose decreased significantly (P<0.05). Serum urea was decreased but there was no significant difference (P>0.05) when the baseline was compared with other timing intervals (Table 3).

DISCUSSION

Rapid emergence from anesthesia and post-operative recovery of cognitive function as well as patient stability is an essential requirement of modern anesthesia.

However, worthy of note is the fact that ruminants are not good subjects for induction of general anesthesia. This is because of the potential danger that may ensue as a result of regurgitation and inhalation of ingesta in these species which is not the case in other monogastric domestic species. Fortunately, their docile temperament permits for the conduct of the majority of surgical procedures by local anaesthesia without the need for pre-anaesthetic sedation. However, in some instances that require complete sedation, with economic justifications, general anaesthesia can be administered and complications will not arise when certain precautionary and safety measures are taken (Taylor, 1991). All the general principles that apply to any animal that is to be given an anaesthetic applied to ruminants. Most general anaesthetic agents; and to a lesser extent the sedatives, induce respiratory and cardiovascular depression and remove normal protective reflexes such as coughing and temperature control (Taylor, 1991). There are some additional problems in ruminants that are not encountered in simple stomached animals which require consideration when anaesthesia of the sheep or goat is contemplated (Taylor, 1991).

Propofol, a non-barbiturate substituted isopropyl phenol is an intravenous anesthetic currently popular in human beings and animals as both a sole agent and as an adjunct in balanced anesthetic techniques (Mazaheri *et al*., 2012). It has been used successfully to induce anesthesia in rabbits at doses of 5-15 mg kg^{-1} of body weight (lipman *et al*., 2008).

This study demonstrates that intravenous Propofol at 4$mgkg^{-1}$ and intramuscular Xylazine at 0.025$mgkg^{-1}$ can be effectively used for general anaesthesia in goats with minimal cardiopulmonary risk. The onset of action was very rapid; however, there were undesirable effects of salivation and urination noticed during surgical plane anaesthesia, this could be due to loss of gastrointestinal reflexes observed virtually in all cases of general anaesthesia (Taylor, 1991). The quality of induction and recovery observed was very good, but surgical plane anaesthesia score was fairly good as reported by Mazaheri *et al*. (2012), but Martin *et al*. (1997) reported having very good surgical plane anaesthesia in a clinical investigation involving children under intensive care observation. It was observed that the rectal temperature and respiratory rates were significantly decreased this is probably due to low metabolic activities as commonly observed in most cases of general anaesthesia Mazaheri *et al*. (2012) reported a contrary finding in an investigations with rabbits using intravenous and intraosseous routes, Abraham *et al*. (1999) reported a decreased in metabolic activities of in an investigation of effects of Propofol on extracellular acidification rates in primary cortical cell culture. The decrease in respiratory rates is likely associated with depression of the pulmonary system due to the effect of the Propofol on the central nervous system. The depression of the respiratory centre and the absence of the response to hypercapnia (Adetunji *et al*., 2002) that can culminate in respiratory acidosis, are reasons why bradypnea occurs. The pulse rates were also decreased slightly without significant difference suggesting milder cardiac response, but the systolic and diastolic blood pressure significantly decreased indicating tissue hypotension this finding is in agreement with findings of Glowaski and Wetmore (1999); Lerche, Nolan *et al*. (2000); Baumgartner, Bollerhey *et al*. (2008), where they reported that Propofol administration induces time and dose-dependent hypotension, negative ionotropy and decreased vascular system resistance, resulting in the decreased cardiac output. The mechanisms by which Propofol induces hemodynamic changes include decreases in preload, afterload and myocardial contractility. Propofol also reduces the baroreceptor reflex set point, allowing slower heart rates, despite decreases in arterial pressure (Glowaski and Wetmore, 1999). The was decreased serum sodium and potassium ions but the changes were not statistically significant this is likely because there were no hemo dilution effects as a result of plasma electrolyte pull from extracellular fluid, renal loss, chelating with anions, and adrenergic stimulation, Gencelep *et al*. (2005) reported a significant findings of decreased potassium ion but not sodium ion during and after Propofol anaesthesia in calves. There was significantly decreased serum calcium, magnesium and hydrogen bicarbonate ion with statistically significant differences, and this could be attributed to decreased myocardial excitability of the heart during surgical plane anaesthesia. The decreased serum calcium and magnesium ion may also be associated with skeletal muscle relaxation due to the effect of Xylazine and Propofol. Carroll *et al*. (1998) recorded a significant decreased in serum HCO_3^- along with decreased arterial blood pH using detomidine-butorphonol-propofol in goats whereas Smith *et al*. (1993) reported a significant decreased in HCO_3^- along with arterial blood pressure after Propofol administration in dogs. There was decreased serum Aspartate Transaminase (AST), Alanine Transaminase (ALT), Albumin (ALB) and urea without statistically significant difference; this is probably due to minimal involvement of hepatic and renal systems as it relates the enzymes involved. Kelawala *et al*. (1999) also reported similar findings in dogs using Propofol alone; however, Brzeski *et al*. (1994) reported that all biochemical parameters remain within physiological limits in sheep under Propofol anaesthesia. A significant decreased in serum Alkaline Phosphatase (ALP), creatinine, total protein and glucose was observed, this may be as a result of active involvement of ALP and creatinine in hepatic metabolism of Propofol and Xylazine, Kelawala *et al*. (1991, 1993) reported increased in serum creatinine during diazepam-propofol-ketamine anaesthesia in goats. The significant decreased of total plasma protein could be as a result of high plasma protein affinity of the Propofol (96-98%) in all species as reported by Cockshott and Douglas (1992) because of the uniform distribution of the Propofol within the blood. Kelawala *et al*. (1991, 1993) reported a contrary finding of significant increased of total plasma protein and albumin also during diazepam-propofol-ketamine anaesthesia in goats. The significant decreased of serum glucose level observed could be due to decreased in metabolic activities following exhaustion of available blood glucose level during initial phase tissue excitement before surgical plane anaesthesia.

It was concluded that combination Xylaxine and Propofol at 0.025$mgkg^{-1}$ and 4$mgkg^{-1}$ respectively can be effectively and safely used for induction and maintenance of anaesthesia in Red Sokoto goats. It was also noted that

recovery was smooth without any violence. The combination was also observed to have minimal effects on the clinico-biochemical parameters of Red Sokoto goats. Further studies should be conducted on the pharmacokinetic activity of the combination in Red Sokoto goats.

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