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Effects of Castration on Epidural Administration of Lidocaine-Tramadol in West African Dwarf (Wad) Goats.

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Summary: Epidural anesthesia is routinely used in ruminants for obstetric manipulations and caudal surgical procedures owing to complications associated with general anaesthesia in this species. Castration is a common farm practice for derived production benefits. The responses of a castrate to anaesthesia may differ from that of an intact animal because of possible anaesthetic-hormonal interplay. This study compared the anaesthetic indices, haemato- biochemical parameters (PCV, Hb, WBC, PLT, Na^{+}, K^{+}, Cl^{-}, urea, creatinine, Cu^{2+}) between castrated and intact goats subjected to epidural anaesthesia with tramadol-lidocaine mixture. Experimental animals were six West African Dwarf (WAD) goats (3 intact and 3 castrated bucks). The drugs were administered into the lumbosacral epidural space. Heart rate, respiratory rate and rectal temperature at 15minutes interval for 90minutes and anaesthetic indices were taken. Blood was obtained for haematology and serum chemistry before drug administration and hourly thereafter for three hours. The onset of drug action in the castrated goats (1.7±0.9 min) compared well with that of the non-castrated goats (2.0±0.0min). However, the duration of analgesia was significantly shorter ($p<0.05$) in the castrated goats (26.7±5.2min) than in the non-castrated goats (83.7±20.8 min), while the duration of recumbency was significantly ($p<0.05$) longer in the castrated goats (23.3 ± 8. 6min) than in the non- castrates (14.8 ± 3.7min). Mean heart rates ranged between 96.0±6.1 to 116.0±16.2 beats/min for non- castrated goats and 94.7±14.8 to 121.0 ±8.1beats/min for the castrated goats. Mean respiratory rates ranged between 60.0±14.4 to 89.3±16.2 breaths/min and 61.0± 31.5 to 122.3±10.0 in the non –castrated and castrated goats respectively. Mean temperature ranged between 39.6±0.4 to 40.8±0.4°C in the non-castrated goats and 40.3±0.3 to 41.4±0.3°C in the castrated goats. Anaesthetic indices and haematobiological parameters were compared using Student's t-test, while physiological parameters were compared using ANOVA for repeated measures. There was reduction in pre-treatment values of some of the haematological, biochemical and hormonal values especially urea in the non- castrate (pre-treatment value-of 22±4.16 and 3-hour post treatment value of 13.3±0.33). The combination of tramadol-lignocaine epidurally is safe in castrate animals as well as in intact animals especially West African dwarf goats as there were no deleterious effects. However, further studies could combine adrenaline for prolonged recumbency when required.

Keywords: Castrate, Epidural, Lidocaine, Tramadol

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INTRODUCTION

Castration, the removal of the testes, is a routine management practice in farm animals especially goats for described production benefits including prevention of inbreeding and removal of buck taint (Yami, 2008). A castrate differs from an intact goat in the testosterone level. The responses of a castrate to anaesthesia may differ from that of an intact animal because of possible anaesthetic-hormonal interplay. Indeed in humans, there have been some reports of decreases in testosterone level following general anaesthesia, possibly because of surgical trauma, but more often an increase occurred one hour after surgery (Cartensen *et al*., 1973).In another study to investigate the reliability of hormone concentrations in hormonal studies following anaesthesia, it was found out that up to 24 h after ketamine/xylazine anaesthesia, any measurements of plasma testosterone concentration, and after anaesthesia and CO2 euthanasia, LHRH concentration, should be treated with caution, as the real effect of the experiment or treatment could be hidden by the anaesthesia and euthanasia.

Ruminants are generally not considered good subjects for general anesthesia mainly because of the hazards of regurgitation and inhalation of ruminal contents or saliva into the lungs if the air way is left unprotected. Other complications associated with general anaesthesia in this species include ruminal tympany and marked cardiopulmonary depression (Taylor, 1999). As a result, regional anesthesia produced by perineural or epidural injections of anaesthetic agents is most frequently employed in this species (Hall *et al.*, 2001; Sadegh *et al.*, 2009). Lumbosacral epidural anesthesia is simple, inexpensive, the most common epidural technique and requires no sophisticated equipment. It is routinely used in ruminants for obstetric manipulations, caudal

surgical procedures and as an adjunct treatment for control of rectal tenesmus (Lee *et al.*, 2003; Sakrda and Tranquilli, 2007).

Tramadol is a synthetic opioid and has been administered via the epidural route in veterinary medicine (Halder and Bose, 2000; Guedes *et al.*, 2005). Two complementary models define its mechanism of action. The first results from the binding of its (+) enantiomer to mu-opioid receptors, whose affinity is about 6000 times less than that of morphine (Fantoni and Mastrocinque 2002; Bozkurt, 2005). However, its main active metabolite, O-desmethyltrama dol,is 6 times more potent than tramadol and possesses a 200-fold greater affinity for mu-opioid receptors (Pypendop and Ilkiw, 2007). The second mechanism involves the inhibition of noradrenaline reuptake by the (-) enantiomer through the increased release of serotonin and inhibition of its reuptake by the (+) enantiomer (Sousa *et al.*, 2007). Various studies suggest that tramadol produces a local and spinal anaesthetic effect while also increasing the postoperative analgesic period and reducing the consumption of analgesics (Delilkan and Vijayan, 1993; Kapral *et al.*, 1999).

Lignocaine is an acetamide local anaesthetic. Local anaesthetics act by blocking signal conduction by altering the fast voltage-gated sodium channels at the neuronal cell membrane (Lemke and Dawson, 2000). Because of its short duration of action, supplemental analgesia using different drugs or re-administration of drugs during surgical operations is usually necessary (Lemke and Dawson 2000; Skarda and Tranquilli, 2007). Opioids and alpha-2 adrenergic agonists are commonly used in combinations with lidocaine resulting in longer and adequate analgesia (Bigham*et al.*, 2009; Rostami and Vesal, 2012).

Tramadol is an analgesic with mixed opioid and non -opioid activities (Garrido et al. 2000) and has been administered into the epidural space alone or with lignocaine in humans (Batra et al., 1999), horses (Natalini and Robinson, 2000), dogs (Guedes*et al.*, 2005; Almeida *et al.*,
2010), cats (Castro *et al.*, 2009) lambs and goats (Dehkordi*et al*, 2012) with demonstration of prolonged analgesia and / antinociception. The mixture of tramadol with lignocaine was therefore chosen as a model in this study for preliminary investigation of possible peculiar effects of extradural anaesthesia on castrated goats in comparison with intact ones. Specifically, this study was to compare the physiological parameters, anaesthetic indices, and haemato- biochemical parameters between castrated and intact goats subjected to epidural anaesthesia with tramadol-lignocaine mixture.

MATERIALS AND METHODS

Animals

Six clinically healthy adult (3 intact and 3 castrated) WAD goats (bucks) were used for this study. The weight range of the goats was between 18 and 24kg with a mean± sem of 21±0.0kg. The goats which were all intact at purchase were obtained at an open market in Ibadan, Nigeria. They were housed together in a large pen that allowed them ample movement. They were fed with concentrates, maize, cassava peelings and unripe plantain. Water was provided ad libitum. The goats were dewormed with boluses of albendazole (Salbezole®, Sam Pharmaceuticals Ltd, Lagos) at an oral dosage of 5mg/kg body weight.

Drugs

Lignocaine hydrochloride (Glocain®, Vital Health Care PVT Ltd, India) which was supplied as 20mg per ml of colourless, aqueous solution without adrenaline in a 20-ml multidose vial. Tramadol hydrochloride (Tramaden®, Laborate pharmaceutical, India) supplied as 100mg in 2ml vial for injection

Experimental design

The goats were randomly allocated to two groups of three animals each. The group tagged the castrate were castrated six weeks before the commencement of the trials using burdizzo as previously described (Yami, 2008). Each animal in both groups was injected extradurally with lignocaine (2.46mg/kg) and tramadol (1mg/kg) mixed in the same syringe. The mean body weight of the castrates was 21.3 ±0.2kg while for the intact goats was 21.4±0.4 kg. The goat's rectal temperature (RT) and respiratory rate (RR) were immediately measured after the epidural injection and subsequently at 15 minutes intervals over a 90-minute period in the course of the trials. Respiratory rate in breaths/min was determined by visual observation of the thoraco- abdominal excursion. Heart rate was measured in beats/min with the aid of a precordial stethoscope. Rectal temperature was determined using a mercury-in-glass thermometer and measured in degrees centigrade (˚C). Venepuncture was done at the jugular vein to obtain blood before drug administration at 1, 2 and 3-hours post administration for haematology and serum biochemistry.

Experimental procedure

The goats were restrained manually on sternal recumbency with the hind limbs extended cranially. An area of 5-7cm was clipped generously and prepared surgically for sterile procedure. The lumbosacral junction was located as described by Hall *et al.*, (2014). In order to achieve a relatively painless epidural puncture, a skin bleb was made over the lumbosacral junction with 0.5ml lignocaine solution.

A 21g hypodermic needle was inserted at the lumbosacral junction (using the pelvic protuberance as a landmark to locate the depression) and then advanced into the epidural space. To confirm the presence of the needle in the epidural space, there was a lack of resistance to the injection of air and absence of spinal fluid in the needle cap. The syringe which contained a

calculated amount of local anaesthetic agent was attached to the needle and then injected over a period of time. The development of motor and sensory blockade was assessed by the goat's inability to stand on its hind limbs. Serial pricking of the skin of the goat's hind limb, perineum, flank and ventral abdomen caudal to the umbilicus with a needle (twenty-one gauge) as in previous studies (Dehkordi*et al*, 2012) was used to determine the onset and extent of analgesia on all or none basis.

Calculations

Onset of action: This was defined as the time interval in minutes between extradural drug injections to hind limb paralysis.

Duration of recumbency: This was defined as the time interval in minutes between onset of hind limb paralysis and ability to stand.

Duration of analgesia: This was defined as the time interval in minutes between time of loss of reflex response in hind limbs, perineum, flank and ventral abdomen to pricking with needle to return of sensation to those parts.

Haematology and serum biochemistry: Haematologic, biochemical and hormonal responses were evaluated from pre- treatment, 1, 2 and 3hours post treatment blood collections.

Statistical Analysis

All data was expressed as Means ± SEM. The mean indices of castrate and intact goats were compared using the student-t-test for paired data. The mean values of the measured physiological parameters were compared using the analysis of variance (ANOVA) for repeated measures followed by the Least Significant Difference (LSD) as post-test. A value of $p \leq 0.05$ was considered significant. Mean values of the haematologic, biochemical and hormonal responses of the castrate and non-castrate goats were compared using student T test.

RESULTS

Observations: Following the administration of extradural anaesthetic solution, neural blockade was consistently achieved in all the experimental goats. All the goats had hind limb paralysis except one castrate which was only mildly ataxic. However, there was a lot of thrashing about by the goats in an attempt to stand up while motor paralysis lasted.

Anaesthetic Indices: The anaesthetic indices of non-castrated and castrated WAD bucks are shown on Table 1. The onset of drug action in the castrated goats (1.7±0.9 min) compared well with that of the non-castrated goats (2.0±0.0 min). However, the duration of analgesia was significantly shorter ($p<0.05$) in the castrated goats (26.7±5.2min) than in the non-castrated goats (83.7±20.8 min), the duration of recumbency was significantly ($p<0.05$) longer in the castrated goats (23.3±8. 6min) than in the non-castrates (14.8±3.7min).

Physiological variables: The mean HR, RR and RT responses of the castrated goats and non- castrated goats after extradural tramadol-lignocaine anaesthesia are shown in Figures 1, 2 and 3 respectively. Mean heart rate ranges were 96.0±6.1 to 116.0±16.2 beats/min for non- castrated goats and 94.7±14.8 to 121.0 ±8.1beats/min for the castrated goats.

Table 1:

Anaesthetic indices of the extradural injection of lignocaine-tramadol in non-castrate and castrated WAD bucks.

	Non-castrate	Castrate
Onset of action (min)	2±0	1.7±0.9
Duration of analgesia (min)	83.7±20.8	26.7±5.2*
Duration of recumbency (min)	14.8±3.7	23.3±8. 6*

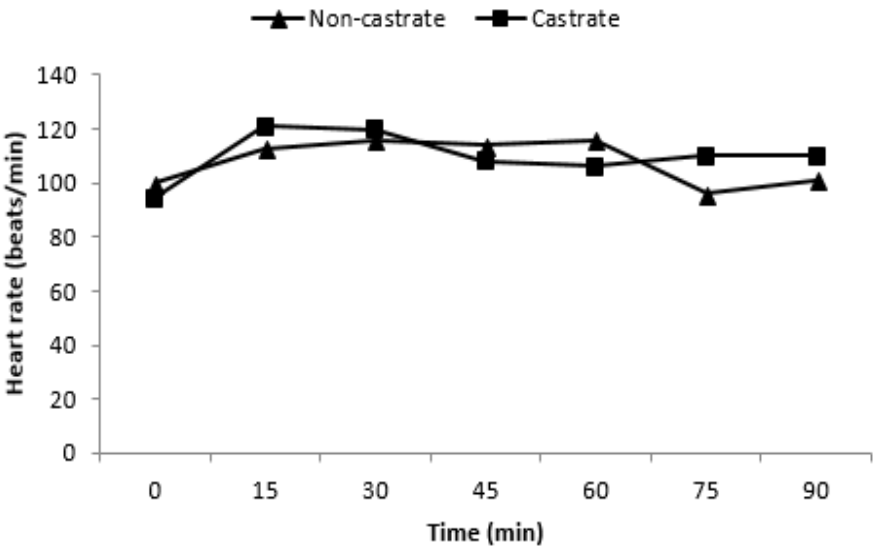

Figure 1.
Heart rate responses of non-castrated and castrated WAD bucks to extradural injection of lignocaine-tramadol mixture

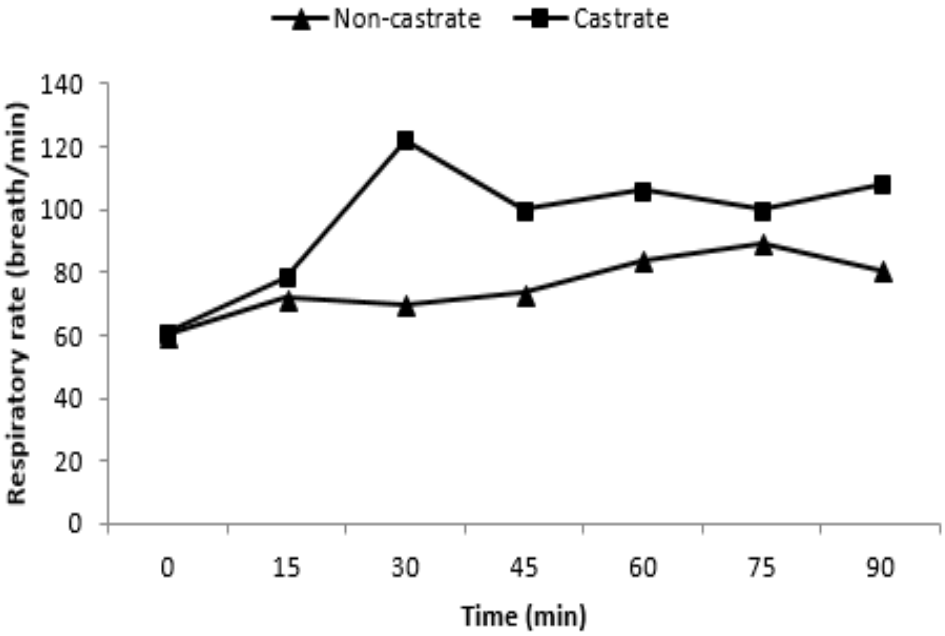

Figure 2.
Respiratory rate responses of non-castrated and castrated WAD bucks to extradural injection of lidocaine-tramadol mixture.

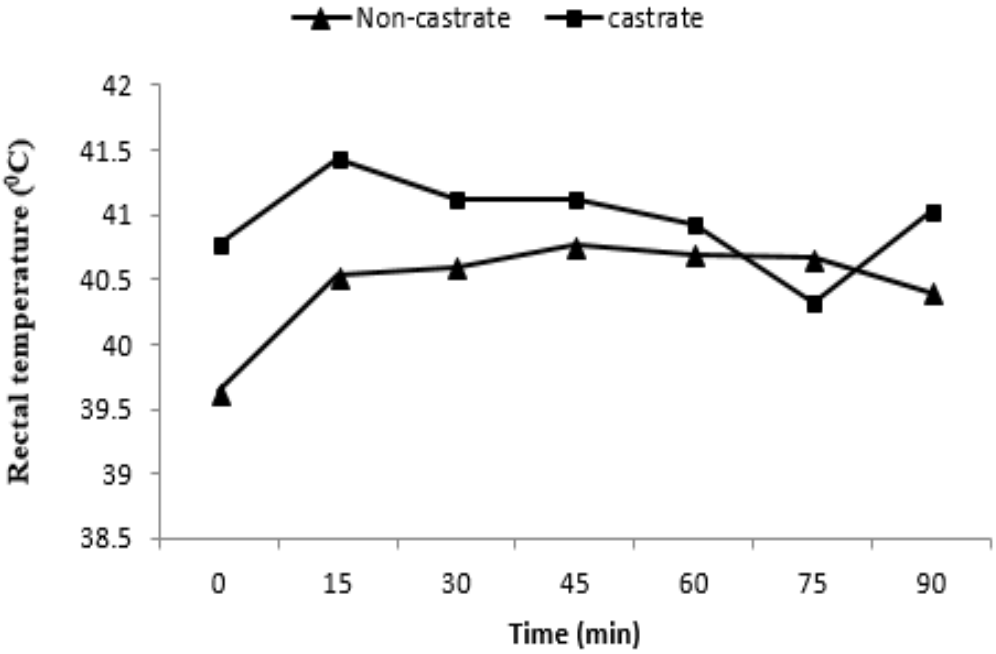

Figure 3
Rectal temperature responses of non-castrated and castrated WAD bucks to extradural injection of lignocaine-tramadol mixture.

Mean respiratory rate ranges were 60.0±14.4 to 89.3±16.2 breaths/min and 61.0± 31.5 to 122.3 in the non –castrated and castrated goats respectively. Mean temperature ranges were 39.6±0.4 to 40.8±0.4°C in the non-castrated goats and 40.3±0.3 to 41.4±0.3°C in the castrated goats.

***Haematology, biochemical and hormonal responses*:** There were flunctuations in the haematological parameters between the castrate and non-castrate goats pre and post treatment (Table 2). However, the castrates showed generally lower haematological values (PCV, Hb, RBC and WBC) than the castrates. The copper values were higher in castrates than the non castrates and showed significant differences ($P \leq 0.05$ and $P<0.01$) at 1 and 2 hours respectively post treatment. Urea values also showed significantly lower differences in non castrates than castrates post administration of tramadol-lignocaine (Table 2).

Table 2:
Haematology, Biochemical and Hormonal responses of non-castrated and castrated WAD bucks following lignocaine-tramadol extradural analgesia.

Parameters	Before Administration	Post-administration		
		1HOUR	2HOURS	3HOURS
PCV (%)				
Non-Castrate	39.33±0.88	33±0.58	39±1.15	30.33±0.67
Castrate	23±1.0	22.67±2.4*	24±1.15***	23±1.15**
Hb (gm/dl)				
Non-Castrate	13.67±0.33	12.3±0.7	15.17±0.6	12±0.57
Castrate	7.2±0.15	7.3±0.6**	8.13±0.41***	7.5±0.32**
RBC ($x10^3$cells/mm^3)				
Non-Castrate	9.33 ±0.176	8.9 ± 0.115	8.6 ±0.057	8.1 ± 0.066
Castrate	3.10 ± 0.078	3.5 ± 0.312**	3.6 ± 0.288***	3.4 ± 0.208****
WBC ($x10^3$cells/mm^3)				
Non-Castrate	9.14 ± 0.44	8.05 ±0.218	8.03 ± 0.034	7.90 ± 0.549
Castrate	4.6 ±0.061	5.61 ±0.337***	5.73 ± 88.19****	5.57 ± 0.463*
PLT ($x10^3$cells/mm^3)				
Non-Castrate	2.83 ±0.167	3.06 ±0.578	2.85 ±0.028	2.39 ±0.170
Castrate	1.19 ±0.056	1.28± 0.332*	1.39±0.165***	1.43 ± 0.233*
Neut (%)				
Non-Castrate	64.33±1.67	64.67±3.18	66±1.16	60.67±0.88
Castrate	63±0.58	63±2.89	64.67±2.23	72±0.58***
Lymp (%)				
Non-Castrate	33.67±1.2	34.67±3.18	31±0.58	36±2.08
Castrate	34.33±2.33	37.33±2.91	34.67±2.6	27±1.16*
Na^+ (mmol/L)				
Non-Castrate	139±1.16	133±0.58	135±1.16	134±0.58
Castrate	136±2.08	138±1.16*	134±2.08	137.67±2.03
K^+ (mmol/L)				
Non-Castrate	3.93±0.07	3.36±0.15	3.43	3.47
Castrate	3.6±0.21	3.86±0.12*	3.5	3.73
CL^- (mmol/L)				
Non-Castrate	106.67±1.67	102.33±1.45	102.33±1.45	102.67±1.45
Castrate	100±2.89	105.33±0.33	100.67±0.67	105±2.89
Urea (mg/dl)				
Non-Castrate	22±4.16	13±1.16	14.33±0.88	13.33±0.33
Castrate	26.33±4.05	29.33±0.88*	19±1.16*	27±4.04*
Creatinine				
Non-Castrate	0.6±0.05	0.4±0.05	0.53±0.03	0.36±0.03
Castrate	0.6±0.05	0.67±0.03*	0.5±0.05	0.63±0.12
Cu^{2+} (mmol/L)				
Non-Castrate	4±0.57	3±0.57	3.33±0.33	3.67±0.33
Castrate	5.27±0.09	5.2±0.21*	6.1±0.16**	5.23±0.03**
Zn^{2+} (mmol/L)				
Non-Castrate	3.33±0.88	2.67±0.33	3±0.58	3.67±0.33
Castrate	3.37±0.15	4.3±0.35*	5±0.06*	3.57±0.41

*P≤ 0.05, **P<0.01, ***P<0.001, ****P<0.0001 - significant compared with the non-castrate

DISCUSSION

The hazardous nature of general anaesthesia in ruminants makes local and regional anaesthesia more favoured in ruminants (Hall *et al*., 2001). Extradural administration of local anaesthetics and some other drugs like opioids, alpha 2 agonists, and ketamine is an established anaesthetic technique for surgeries caudal to the diaphragm (Hall *et al.,* 2001; Habibianah *et al.*, 2011). Results from this study showed that extradural lignocaine-tramadol mixture produced a longer duration of analgesia but a shorter duration of recumbency in the non-castrated compared with the castrated goats (Table 1). However, the onset of drug action was similar in both groups(Table 1). the long duration of analgesia of 83.7±20.8 min in the non-castrate goats is much longer than the established duration of about 60 minutes by plain lignocaine (Hall *et al*, 2001). This prolonged analgesia is clearly attributable to tramadol in the mixture. Furthermore, this finding is consistent with a longer duration of analgesia with tramadol-lignocaine than lignocaine alone without any side effects in previous similar studies (Natalini and Robinson, 2000; Bigham*et al.* 2010; Dehkordi*et al*, 2012; Marzok and El-Khodery, 2015). It is interesting that the duration of recumbency of the two groups of goats studied was very short (Table1). Reasons for this could be because of the absence of adrenaline which usually causes

vasoconstriction thereby prolonging the duration of action of lignocaine (Hall *et al.,* 2001).

In addition to this, about a half of the usual dosage of lignocaine was used since its use was in combination with another drug. The dosages employed in this study were as used in a previous study in goats (Dehkordi*et al.,* 2012). Furthermore, opioids are known to block only the sensory neurons and their sole use as epidural anaesthetics result in analgesia without hindlimb paralysis (Habibianah*et al,* 2011). Epidural anaesthesia may result in changes in heart rate and blood pressure as a result of sympathetic blockade (Veering and Cousins 2000). The HR, RR, and rectal temperature were not significantly different in comparison with baseline values throughout the study. This is in agreement with previous results reported following extradural tramadol in combination with lignocaine in cattle (Bigham*et al.,* 2010). Although, the castrate goats exhibited a rise and fall trend especially in the respiratory rate and rectal temperature (Fig 2, 3) which might be due to higher excitability of the castrate and the drug effects. These findings suggest that both epidural injections of tramadol and lignocaine did not produce adverse significant cardio-depressant effect in goats and further supported the safety of epidural tramadol injections as earlier reported in dogs, pigs and cattle (Alonso *et al.,* 2005; Ali *et al.,* 2010; Ajadi *et al.,* 2012). There were fluctuations in the hematological values post administration of epidural tramadol- lignocaine which might be attributed to the drug and testosterone level differences between the castrate and non-castrate. However, the reduced hematological result in the castrate has been earlier reported that reduction of normal serum testosterone levels as in castrated animals is associated with suppression of erythropoiesis (Olaifa and Akpan, 2017).

The reduction in Hb, PCV, RBC and WBC in the non-castrate could also be due to blood pooling into the reservoir like spleen as a result of the administered drugs. Copper plays an important role in body metabolism, largely because it allows many critical enzymes to function properly (Harris, 2001). Copper is essential for maintaining the strength of the skin, blood vessels, epithelial and connective tissue throughout the body. Cu plays a role in the production of hemoglobin, myelin, melanin and it also keeps thyroid gland functioning normally (Groff *et al.,* 1995; Harris, 2001).

Maintaining the proper dietary balance of Cu, along with other minerals such as zinc and manganese, is important (Araya *et al.,* 2006). Copper level of castrate animals was significantly higher than in intact animals at the 2nd hour post administration. This transient copper accumulation might be due to reduction in the synthesis of the copper transporter protein ceruloplasminto cause failure of excretion of copper into bile and it accumulates in body tissues and this could lead to major hepatic and neurological involvement in chronic accumulation (Bhalerao *et al.,* 2016). Serum urea level increases significantly an hour post administration in the castrate which depicts a transient suppression of urea excretion by the kidneys although there were no clinical adverse effects observed. There were fluctuations in the zinc level but not significant meaning no negative effects of the drugs on zinc metabolism.

It could be concluded from this research that epidural administration of tramadol-lignocaine combination in castrate is beneficial as the onset of action is fast and the duration of recumbency is short in both castrate and non-castrate which means quick recovery of the goats following procedures. Also, this combination is safe in castrate animals as well as in intact animals especially West African dwarf goats as there were no deleterious effects. However, further studies could combine adrenaline for prolonged recumbency when required.

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