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Influence of Tramadol on Anaesthetic Indices and Physiological Parameters of Epidural Lignocaine in West African Dwarf Sheep Undergoing Laparo-Ovariectomy

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Summary: The influence of tramadol on the anaesthetic indices and physiological parameters of epidural injection of lignocaine was evaluated in West African Dwarf (WAD) sheep undergoing laparo-ovariectomy. Ten female sheep weighing (16.2 ± 1.3 kg) were randomly allocated into anaesthesia with epidural injection of lignocaine (4mg/kg) (LIG), or lignocaine (2mg/kg) and tramadol (2mg/kg) (LIG-TRA). Following anaesthesia, they were aseptically prepared and subjected to laparo-ovariectomy. Behavioural changes were noted as they occur, and onset of drug action (OAN) (time between epidural injection and loss of pedal reflex), duration of analgesia (DAN) (time between disappearance and reappearance of pedal reflex) were determined. Also, duration of recumbency (DRC) (time between loss of righting reflex and returns to sternal recumbency) and recovery time (RCT) (time between re-appearance of pedal reflex and when the animal was able to stand without ataxia) were determined. Rectal temperatures (RT), respiratory rates (RR) and heart rates (HR) were determined every ten minutes for two hours. Results were expressed as mean ± standard error of mean. Anaesthetic indices were compared with Student's t-test, while physiological parameters were compared with analysis of variance (ANOVA) for repeated measures. In this study, one sheep anaesthetized with LIG-TRA had bloat while none in sheep anaesthetized with LIG had bloat. The OAN was significantly ($p < 0.05$) shorter in LIG-TRA (1.4 ± 0.5 mins) than with LIG (4.4 ± 2.8 mins). Although DAN and DRC were longer in LIG-TRA (133 ± 19.5 mins, 192.6 ± 43.6 mins) than LIG (119.4 ± 52.5 mins; 166.2 ± 30.6 mins) respectively, values were not statistically significant ($p = 0.863$). In addition, RCT was longer in LIG-TRA (56.0 ± 48.6 mins) than LIG (34.0 ± 20.6 mins). The RT, RR and HR did not differ significantly ($p > 0.05$) between LIG-TRA and LIG, and as well as throughout the duration of study. It was therefore concluded that tramadol did not appear to improve the anaesthetic indices of epidural lignocaine injection in sheep but increased the duration of recumbency with the tendency to cause bloat.

Keywords: Epidural, Lignocaine, Tramadol, Sheep, Anaesthesia

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INTRODUCTION

Laparotomy is an invasive surgical procedure into the abdominal cavity that allows visual examination of abdominal organs and documentation and correction of pathologic abnormalities (Al- Sobayil & Ahmed, 2007; Hendrickson, 2007). Generally, it constitutes the single largest group of surgical operations carried out in ruminants (Haskell, 2004). Laparotomy is indicated for exploration of abdominal and pelvic cavities and other surgical procedures involving abdominal and pelvic organs. Other specific indications are caesarean section, embryo transfer, rumenotomy, ovariectomy, abomasotomy, ventral abdominal herniorrhaphy (Nuss *et al.*, 2006; Teixeira *et al.*, 2011).

Traditionally, regional anaesthesia is commonly used in ruminants undergoing flank surgery. This may be achieved through the administration of local anaesthesia into the epidural space. An effective epidural block has been shown to attenuate the neuro-humoral stress response to surgery, thus reducing post-operative cardio-respiratory functions and minimizing complications (Veering and Cousins, 2000). Although several local anaesthetics are available for epidural application, the most commonly used substance is lignocaine (Adetunji *et al.*, 2001).

Epidural injection of lignocaine is characterized by rapid onset of actions, however due to the short half-life; lignocaine does not provide satisfactory post-operative analgesia. Adrenaline is often added to lignocaine preparation in order to cause vasoconstriction of the blood vessels within the epidural space and slowed down the uptake of the drug into circulation. This invariably increases the duration

of action of lignocaine. Other agents such as bupivacaine are also associated with prolong duration of recumbency which makes them not appropriate for use in day-cases.

Tramadol is an analgesic with mixed opioid and non-opioid activities (Garrido *et al.*, 2000). The non-opioid activity is mediated through alpha-2-agonist and serotonergic activity. Tramadol has been reported to cause less respiratory depression compared with morphine or other opioid analgesics (Bhattacharya *et al.*, 2005; Natalini *et al.*, 2007). This was thought to be due to its weak binding to μ opioid receptors, and its monoaminergic action which partially antagonizes the μ opioid receptors. The epidural effect of tramadol in cattle was described to have no significant effect on heart rate, respiratory rate and rumen motility (Ali *et al*., 2010).

Epidural injection of tramadol has been evaluated in goats undergoing castration (Ajadi *et al.*, 2012). The drug was found to be characterized by shorter duration of analgesia. However, it was found to be beneficial in the sense that it allows the animals to remain standing unlike lignocaine which makes the animal recumbent. Thus, it is presumed that combination of tramadol and lignocaine will produce better effect than either lignocaine or tramadol alone.

Epidural injections of combinations of lignocaine and tramadol have been evaluated in goats, sheep and water buffalo (Habiban *et al.*, 2011; Dehkordi *et al.*, 2012; Ayman *et al.*, 2015). The combination was found to produce a significantly longer duration of analgesia compared with epidural lignocaine injection alone. However, these trials all make use of plain lignocaine. In routine field practice, lignocaine injection containing adrenaline is often used in order to prolong the duration of action of lignocaine. Therefore, it is important to know whether lignocaine-tramadol combination truly has advantage over lignocaine containing adrenaline injection. This study therefore seeks to compare the epidural effect of lignocaine and lignocaine-tramadol on the anaesthetic and cardiopulmonary parameters of sheep undergoing laparo-ovariectomy.

MATERIALS AND METHODS

Animals

Ten intact female adult West Africa Dwarf (WAD) sheep with mean weight 16.2 ± 1.3 kg were used for this study. The sheep were kept in Small Ruminant Unit at the College of Veterinary Medicine, Federal University of Agriculture, Abeokuta. They were fed grasses and supplements and water was provided *ad-libitum*. Before the commencement of the study, the animals were judged to be clinically healthy based on findings at physical examination and results of complete blood count. The study was approved by the Ethical and Animal Care and Use Committee of the College of Veterinary Medicine, Federal University of Agriculture, Abeokuta.

Drugs

- Lignocaine hydrochloride + Adrenaline (Lignovit 20-AH^{R}, Vital Healthcare PVT LTD, Nashik, India) supplied as a 2% (20mg/ml) of clear colourless solution in a 50ml multidose bottle.
- Tramadol hydrochloride (Tramadol^{R}, Gland Pharma, India) supplied a 5% (50mg/ml) clear colourless solution in 2ml ampoule.

Experimental Design

This study used a simple randomized design and observers were blinded of the drug regime that was employed. The sheep were randomly assigned to two groups of five animals each.

- Sheep in Group A were anaesthetized with an epidural injection of Lignocaine at the rate of 4mg/kg while
- Sheep in Group B were anaesthetized with epidural injection of 2mg/kg of 2% Lignocaine and 2mg/kg 5%Tramadol). All epidural injections will be administered into lumbosacral space by a trained Veterinary Surgeon.

Experimental Procedure

The Sheep were weighed and the lumbosacral area was prepared aseptically for epidural injection. They were manually restrained for the epidural injection and a 19 gauge needle was inserted into the epidural space. Once, it is confirmed that the needle is in the epidural space, the drugs were injected. Once epidural injection was successful, sheep were monitored until they assumed sternal recumbency. Following confirmation of loss of pedal withdrawal reflex, laparo-ovariectomy was done on the animal using flank approach. Pain associated behavioural changes such as phonation, restlessness (defined as non-purposeful movement associated with bleating) urination and defecation were noted from the start of laparo-ovariectomy until the animal recovers. Changes were evaluated by an observer. Response to noxious stimulus, the time and course of events and selected physiological measurements such as heart rate, respiratory rate and rectal temperature were recorded. Noxious stimulus was tested with the application of artery forceps (Closed to the third ratchet) at the skin around the hock or the carpus. All four limbs were tested. The response was considered positive when there was withdrawal of the limb or movement of any part of the body. Stimuli were repeated every five minutes until a positive response is recorded.

Anaesthetic Indices

- Onset of Action (Time interval between time of epidural injection and loss of righting reflex).
- Duration of Recumbency (Time interval between time of lateral recumbency and standing).

- Duration of Analgesia (Time interval between disappearance of pedal reflex and return of pedal reflex).
- Duration of Surgery (Time interval between start of surgery and end of surgery).
- Recovery time (Time interval between return of pedal reflex and when the animal assumes standing without ataxia).

Physiologic Parameters Physiological measurements which included heart rate were determined with cardiac stethoscope. Respiratory rate was determined by using abdominal excursion, and rectal temperature using a clinical thermometer. Measurements were recorded immediately after epidural anaesthesia and at 10 minutes intervals over a period of 120 minutes.

Statistical Analysis

Data distribution was tested for normality by constructing frequency histograms of data series. Data with a normal distribution was expressed as mean ± (SD). Anaesthetic indices between treatments were compared using Student's t-test. Physiological parameters were compared both for differences within and between treatments using ANOVA for repeated measures. Least square differences were used for post-hoc analysis. All statistical analysis was performed using SPSS 17.0 software (SPSS Inc., Chicago IL, USA). A value of $p < 0.05$ was considered significant.

RESULTS

Observation

All the sheep were recumbent regardless of the type of drug and did not show any sign of chewing or rumination. The only adverse effects observed were defecation, urination and bloat (Table 1). Bloat was observed only in one sheep that was anaesthetized with epidural injection of lignocaine-tramadol.

Anaesthetic Indices

The onset of drug action was significantly ($P < 0.05$) shorter in sheep anaesthetized with epidural lignocaine-tramadol injection compared with sheep

Table 1: Adverse effects of epidural lignocaine or lignocaine-tramadol in WAD sheep undergoing laparo-ovariectomy

Adverse effects	Lignocaine group	Lignocaine-Tramadol group
Defecation	+ (5)	+ (5)
Urination	+ (3)	+ (3)
Arrhythmia	- (5)	- (5)
Apnoea	- (5)	- (5)
Cyanosis	- (5)	- (5)
Hypothermia	- (5)	- (5)
Hyperthermia	- (5)	- (5)
Bloat	- (5)	+ (1)

Keys+ = Present; - = Absent; No. of sheep in parenthesis

Table 2: Anaesthetic indices of epidurally administered lignocaine or lignocaine-tramadol mixture in WAD sheep undergoing laparo-ovariectomy

Anaesthetic Indices	Lignocaine group (n=5).	Lignocaine-Tramadol group (n=5).
Onset of Action (mins)	4.4 ± 2.8	1.4 ± 0.5
Duration of Recumbency (mins)	166.2 ± 30.6	192.6 ± 43.6
Duration of Analgesia (mins)	119.4 ± 52.5	133 ± 19.5
Duration of Surgery (mins)	42.2 ± 9.3	45.8 ± 9.4
Recovery Time (mins)	34 ± 20.6	56 ± 48.0

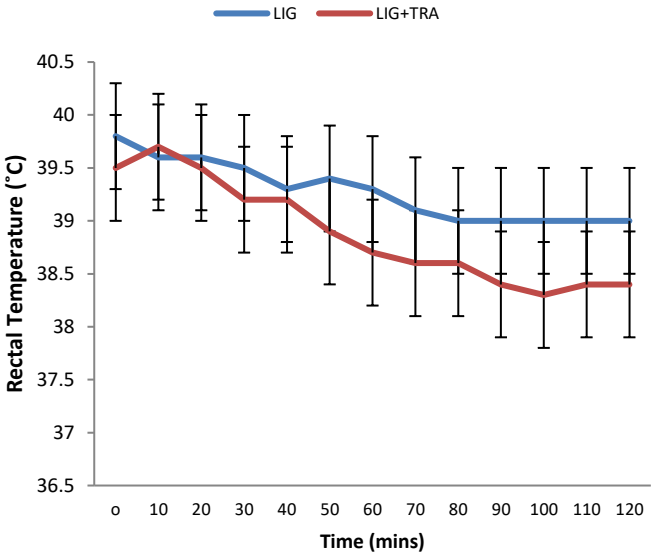

Figure 1: Changes in Rectal temperature following epidural lignocaine or lignocaine-tramadol in WAD sheep undergoing laparo-ovariectomy

epidural injection of lignocaine and that of lignocaine-tramadol mixture. Although the duration of recumbency was longer in lignocaine-tramadol sheep, than sheep anaesthetized with lignocaine, the values were not significant ($P > 0.05$). Similarly, duration of surgery and recovery time was not significantly different between sheep anaesthetized with lignocaine and those anaesthetized with lignocaine-tramadol (Table 2).

Physiological Parameters

The rectal temperature tended to decrease progressively in sheep anaesthetized with either lignocaine or lignocaine-tramadol injection throughout the duration of study (Figure 1). However, there was no significant difference in the rectal temperature between lignocaine and lignocaine-tramadol anaesthetized sheep. Also, there was no significant difference in temperature throughout the duration of monitoring.

Similarly, the respiratory rate tended to increase in sheep anaesthetized with either epidural lignocaine or lignocaine-tramadol injection (Figure 2). However,

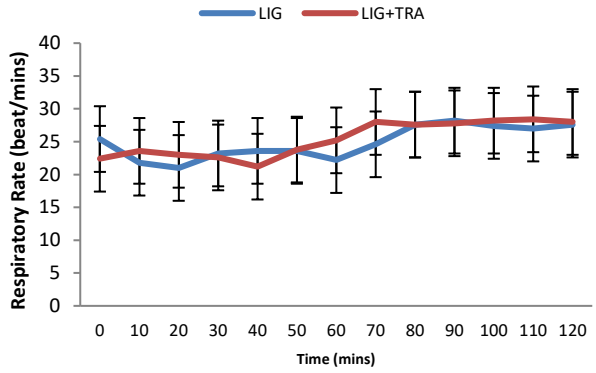

Figure 2: Changes in Respiratory rate following epidural lignocaine or lignocaine-tramadol in WAD sheep undergoing laparo-ovariectomy.

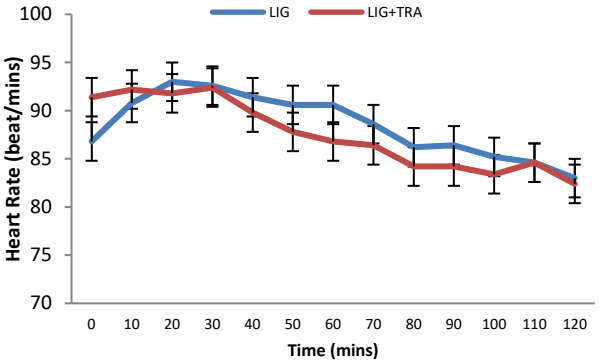

Figure 3: Changes in Heart rate following epidural lignocaine or lignocaine-tramadol in WAD sheep undergoing laparo-ovariectomy

there was no significant difference in the respiratory rate between lignocaine and lignocaine-tramadol anaesthetized sheep. Also, there was no significant difference in respiratory rate throughout the duration of monitoring.

In addition, the heart rate of sheep anaesthetized with either epidural injection of lignocaine or lignocaine + tramadol increased up to 20 minutes after which it then decreases progressively throughout the duration of study (Figure 3). However, there was no significant difference in the heart rates between lignocaine and lignocaine-tramadol anaesthetized sheep. Also, there was no significant difference in heart rate throughout the duration of monitoring.

DISCUSSION

This study showed that epidural injection of a combination of Lignocaine and tramadol in sheep undergoing laparo-ovariectomy appeared to provide a better perioperative analgesia characterized by rapid onset and longer duration of analgesia than epidural injection of Lignocaine alone. In addition, the combination is characterized by longer duration of recumbency and recovery time when compared with epidural lignocaine alone.

Lignocaine hydrochloride is the most commonly used local anaesthetics for epidural analgesia in humans and animals. The drug is characterized by rapid onset with short duration of action making it not suitable for medium to long term surgery. Epidural injection of lignocaine in West African Dwarf sheep in this study was characterized by somewhat longer duration of analgesia than reported for goats (Umar and Gapsiso, 2008) but similar to that reported for sheep (Lucky *et al*., 2007). This finding may suggest a specie difference in the response of animal to epidural drug administration.

Tramadol has been used epidurally in humans for many years, but in veterinary medicine epidural administration of tramadol have been studied in horses, dogs, cattle, goat, sheep and water buffalo (Natalini and Robinson 2000; Alonso *et al.* 2005; Ali *et al.* 2010, Habiban *et al.*, 2011; Ajadi *et al*., 2012; Ayman *et al.*, 2015). Noradrenergic descending pathways and serotoninergic system innervate all levels of the spinal cord, and can modulate afferent pain signals at this level (Alonso *et al*., 2005). Opioids, noradrenergic and serotoninergic drugs can interact with these systems to produce antinociception. Epidural tramadol is characterized by long duration of analgesia and absence of ataxia thus enabling the animal to remain standing during the course of anaesthesia (Habiban *et al.*, 2011; Ajadi *et al*., 2012; Ayman *et al.*, 2015). This is an advantage over drugs like lignocaine and bupivacaine

The technique of administering two or more drugs to facilitate the induction and maintenance of anaesthesia has gained considerable popularity (Ajadi *et al*., 2007). The goal of this combination is to achieve more specific target response and minimize the side effects of individual drugs. In a previous study, epidural injection of lignocaine alone was characterized by short onset of anaesthesia and longer duration of recumbency, while epidural injection of tramadol in goats had the advantage that the animals remain standing but with poor quality of analgesia (Ajadi *et al*., 2012). In previous study, epidural combination of lignocaine and tramadol was reported to have a significantly longer duration of analgesia compared with lignocaine injection alone (Habiban *et al*., 2011; Ayman *et al.*, 2015). However, all these trials involved the use of plain lignocaine. Thus, in the current study, lignocaine injection containing adrenaline was used.

In this study, sheep anaesthetized with epidural combination of lignocaine and tramadol had a shorter onset of action and longer duration of analgesia compared to epidural lignocaine injection alone. However, the duration of action lignocaine-tramadol combination was not significantly different from that of lignocaine injection alone. This finding was contrary to that observed previously in goat, lamb and water buffalo (Habiban *et al.*, 2011; Ayman *et al.*, 2015) and may be due to the preparation of lignocaine that was used. In the previous studies, plain lignocaine was used for epidural injection, while in the current

study, lignocaine containing adrenaline was used. In addition, the combination was characterized by longer duration of recumbency and recovery period. The longer duration of recumbency and recovery period is a disadvantage as the sheep will have to be monitored for a longer duration of time. It also implies that the sheep will be prone to developing post-anaesthetic bloat.

Both epidural injection of lignocaine and lignocaine–tramadol combination was characterized by virtual lack of adverse reaction in this study. This suggests that the combination is safe to use in animals. The only adverse reaction observed was bloat and it was noticed in one of the sheep anaesthetized with epidural injection of lignocaine and tramadol. The bloat may be secondary to ruminal stasis as a result of long duration of recumbency. This will be a disadvantage to the use of the combination in ruminants.

Surgery may activate a neuroendocrine stress response that is associated with sympathetic stimulation and increases in heart rate and blood pressure (Nieuwoudt *et al.*, 2006). One disadvantage of epidural anaesthesia is the effect on the cardiovascular system (Stegmann, 2009). Epidural anaesthesia may result in changes in heart rate and blood pressure as a result of sympathetic blockade (Veering and Cousins, 2000). In this study, treatment with either epidural tramadol or lignocaine did not significantly alter the heart rate, respiratory rate and rectal temperature in sheep subjected to laparo-ovariectomy throughout the monitoring period. The rectal temperatures tended to decrease progressively probably due to the heat loss from body cavity as a result of the laparotomy. This finding is contrary to the previous studies in which the temperature remained unchanged throughout the duration of anaesthesia (Habiban *et al.*, 2011; Ayman *et al.*, 2015). Also, the respiratory rate tended to increase while the heart rate tended to decrease in this study contrary to previous studies. This might also be connected to the neuroendocrine stress response associated with surgery.

In conclusion, epidural injection of lignocaine-tramadol did not appear to have any advantage over epidural injection of lignocaine alone when the lignocaine preparation contains adrenaline. However, the combination had longer duration of recumbency and recovery period making the animal prone to developing post-anaesthetic ruminal tympany. It will thus appear that the combination did not have any beneficial effect over epidural lignocaine injection in sheep.

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