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Potentiating the Epidural Analgesic Effect of Lidocaine in Uda Sheep with Xylazine and Medetomidine

Shittu Shamsudeen[1], Sherifat Banke Idris[1*], Adamu Abdul Abubakar[2,3], and Mayaki M. Abubakar[4]

[1]Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary Medicine Usmanu Danfodiyo University, Sokoto, Nigeria

[2]Department of Veterinary Medicine, College of Applied Health Sciences A'Sharqiyah University, Sultanate of Oman

[3]Department of Veterinary Surgery and Radiology, Faculty of Veterinary Medicine, Usmanu Danfodiyo University, Sokoto, Nigeria

[4]Department of Veterinary Medicine, Faculty of Veterinary Medicine Usmanu Danfodiyo University, Sokoto, Nigeria

***Corresponding Author:** Sherifat Banke Idris, **E-Mail:** bankidris67@gmail.com

ABSTRACT

This study was undertaken to compare the analgesic effects of lidocaine, xylazine, and medetomidine alone and their combinations with lidocaine in Uda sheep. The sheep (n = 6) were assigned to five different epidural treatment groups using a cross-over design with a wash-out period of one week between the treatment groups. The group (A) received lidocaine at 2.86 mg/kg, the group (B) received xylazine at 0.05 mg/kg, the group (C) received medetomidine at 20 µg/kg, the group (D) received lidocaine-xylazine combination at 2.15 mg/kg and 0.125 mg/kg, respectively, and the group (E) received lidocaine-medetomidine combination at 2.15 mg/kg and 5 µg/kg, respectively. The analgesic effect was evaluated by the needle-prick test method. The onset and duration of analgesia in the mentioned regions were recorded. Ataxic and sedative effects were carefully observed and recorded according to the scoring system. Blood was collected at baseline (0), immediately after onset, and 24 hours post-administration. Results showed that medetomidine treatment produced a highly significant ($p < 0.01$) earlier onset of action (6–8 min) than the rest of the treatment groups. Medetomidine treatment also produced a significantly ($p < 0.001$) longer duration of analgesia (190-230 min) than the rest of the treatment groups. Lidocaine alone or in combination with xylazine or medetomidine induced severe ataxia, while xylazine and medetomidine alone or in combination with lidocaine produced mild to moderate sedation. In conclusion, epidural administration of medetomidine, lidocaine-xylazine, and xylazine produced a prolonged, longer duration of analgesia with useful systemic sedation in sheep.

Keywords: Epidural analgesia, Lidocaine, Medetomidine, Uda sheep, Xylazine.

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INTRODUCTION

In general, ruminants are not considered suitable subjects for general anesthesia, primarily due to the possibility of regurgitation and inhalation of ruminal contents or saliva into the lungs if the airway is left unprotected with an endotracheal tube. Thus, in these species, regional anesthesia provided by perineural or epidural injection of anesthetic agents is used most frequently **(Hall and Clarke, 2001).** Epidural anesthesia techniques are comparatively simple, safe, efficient and economical, as they do not require the use of sophisticated equipment **(Lucky *et al*., 2007).** Therefore, these advantages make it the most frequently used technique for the treatment of different obstetrical and surgical interventions caudal to the diaphragm **(Lucky *et al*., 2007).**

Lidocaine, which is the most frequently used agent to induce epidural anesthesia in ruminants, has a delayed onset and short duration of action and produces hind limb paralysis, which is a common and undesirable side-effect **(Skarda and Flakes, 2007; Habibian *et al., 2011*; Zayed *et al., 2020*).** For procedures requiring long-duration analgesia, epidural administration of lidocaine combined with other agents that will give a longer duration of action is more appropriate **(Skarda and Flakes, 2007; Zayed *et al*., 2020)**. Researchers have hypothesized that opioids and alpha-2

adrenoceptor agonists which selectively block sensory fibres, can be combined with lidocaine to provide a longer duration of analgesia with a decreased likelihood of rear limb dysfunction **(Dehkordi *et al*., 2012; Rostami *et al*., 2012).** Alpha-2 adrenoceptor agonists, such as xylazine and detomidine, are sedative-hypnotics used as sedatives, analgesics and premedicants **(Bouchenafa and Livingston, 1987).**

The epidural administration of alpha-2 adrenoceptor agonists is an analgesic alternative to opioids **(Pohl *et al*., 2012)** and produces most of its antinociceptive effects by stimulating alpha-2 adrenoreceptors in the dorsal horn of the spinal column, which inhibits nociceptive neurons and reduces the release of substances. **(Jaakola *et al*., 1991; Sinclair, 2003).** Xylazine (N-(2,6-dimethylphenyl)-5-6-dihydro-4H-1,3-thiazine-2amine), one of the alpha-2 adrenoceptor agonists, has potent sedative, analgesic, and muscle relaxant activity. It has been used in veterinary practice as a sedative-analgesic and neuraxially for analgesia in many species **(Grubb *et al*., 2002; DeRossi *et al*., 2003).** Medetomidine, a 4(5)-[1-(2,3-dimethyl phenyl)-ethyl] Imidazole is a full alpha 2-adrenoceptor agonist with more lipophilicity, selectivity, potency, and efficacy than other alpha 2-adrenoceptor agonists **(Mpanduji *et al*., 2001; Singh *et al*., 2005).** Epidural administration of medetomidine has been shown to provide prolonged analgesia in cows, but it was accompanied by significant cardiopulmonary depression **(Lin *et al*., 1998).**

Also, the adverse effects of anesthesia and/or analgesic agents on hemo-biochemical parameters have previously been identified. **Ismail *et al*., (2010) and Lokhande and Aher (2018)** reported that epidural administration of lidocaine and lidocaine-xylazine combinations produces effects on the values of hemato-biochemical parameters, particularly packed cell volume (PCV), total erythrocyte count (TEC), total leucocyte counts (TLC), lymphocyte count, aspartate transaminase, alanine transaminase, blood urea nitrogen and serum creatinine in sheep and cattle, respectively.

The present study aimed to compare the lumbosacral epidural analgesia and hemo-biochemical changes produced by lidocaine, xylazine, and medetomidine alone and their combinations with lidocaine in Uda sheep.

MATERIALS AND METHODS

Six clinically healthy non pregnant Uda ewes with average body weight of 27.20 ± 7.90 kg (M±SD) and aged (1-2) years were used. They were housed in the Usmanu Danfodiyo University/Veterinary Teaching Hospital's small ruminant pens. They were acclimatized for two weeks during which deworming and prophylactic antibiotic treatment were administered. The sheep were fed on hays, wheat bran and beans husks. Water was also provided *ad libitum*. The sheep were assigned to five treatment groups in a cross-over design with a washout period of one week between the treatments as shown in **Table 1.**

Table 1: Experimental Animal Grouping:

Groups	Number of sheep (n)	Treatment
A	6	Lidocaine HCl
B	6	Xylazine
C	6	Medetomidine
D	6	Lidocaine - xylazine
E	6	Lidocaine - medetomidine

Analgesic Qualities

The analgesic effect was evaluated by the needle prick test method using a 21 gauge needle **(Zayed *et al*., 2020).** The pain response was assessed in the pelvic limbs, perineum, pelvic- abdominal and thoracic regions. A positive response was defined as avoidance of movements of head, neck, trunk, limbs, tail, attempts to kick, and turning of the head toward the stimulation site **(Marzok and El-khodery, 2015).** The needle prick test was measured each minute until no reaction occurred (onset of analgesia) and then at 5, 10, 15, 30, 45, 60, and 90 mins (duration of analgesia). For animals where analgesia lasted more than 90 minutes, further evaluation was performed every 30 minutes until recovery **(Zayed *et al*., 2020).** The evaluation of pain was graded on four- point scale in each sheep **(Zayed *et al*., 2020)** as follows:

0 - Abolished response
1 - Very weak response
2 - Moderate response
3 - Strong response

Evaluation of Ataxia

The sheep were evaluated for ataxia post-administration of the treatments by walking them around after the onset of analgesia was established and these were assessed at 5, 10, 15, 30, 45, 60, 90, 120, 150 180, 210, and 240 minutes post-administration. The evaluation of ataxia was graded on four- point scale in each sheep **(Marzok and El-khodery, 2015)** as follows:

0 - No incoordination.
1 - Mild (slight incoordination of the hind quarter).
2 - Moderate (walking but very ataxic).
3 - Severe (falling).

Evaluation of Sedation

The sheep were evaluated for sedation post-administration of the treatments after the onset of analgesia was established and were assessed at 5, 10, 15, 30, 45, 60, 90, 120, 150 180, 210, and 240 minutes post-administration. Sedation was graded on a four-point scale in each sheep according to **(Marzok and El-khodery, 2015)** as follows:

0 - Alert (no sedative effect).
1 - Mild sedation (reduced alertness with no other signs).

2 - Moderate sedation (drowsiness and slight drop of head, lips, and upper eyelids).
3 - Deep sedation (marked drowsiness and drop of head).

Evaluation of Hemato-Biochemical Parameters

Blood samples (5 mL: Include 2 mL for hematological analysis and 3 mL for biochemical analysis) were collected from the jugular vein of each animal into a sterile blood sample bottle containing EDTA (Hcelos® health diagnostic) for hematological analysis and plain sample bottle (Hcelos® health diagnostic) for biochemical analysis. Blood samples were collected from the jugular vein at baseline, after onset of analgesia, and 24 hours post administration for evaluation of haemato-biochemical changes **(Lokhande and Aher, 2018).** Hematological parameters including hemoglobin concentration (Hb), packed cell volume (PCV), red blood cell counts, total and differential leucocytes counts were examined using an automated haematology analyzer (Mythic 22 Orphee, Switzerland), while biochemical parameters including blood urea nitrogen (BUN), creatinine (Cr), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were examined using a spectrophotometer.

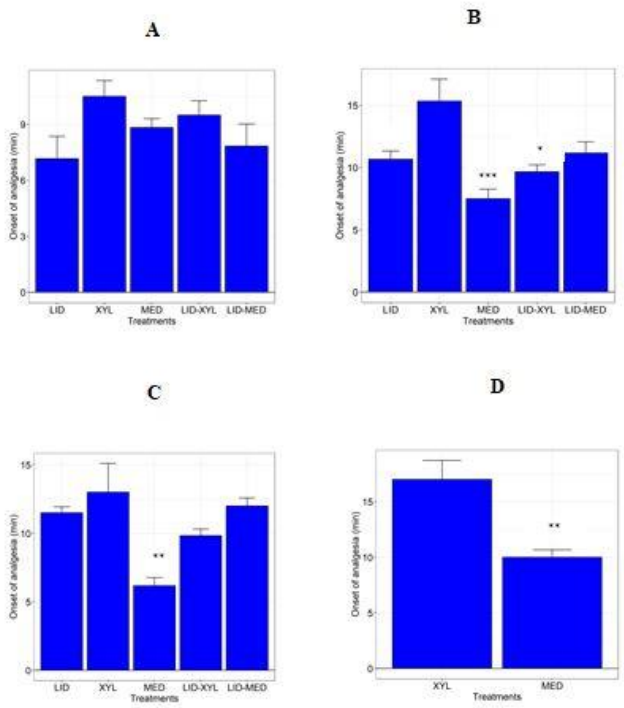
Statistical Analysis

Data generated were tested for normality before analysis using a normal probability plot. All data were expressed as mean ± SD except for ataxia and sedation data for which non-parametric test was used for their comparison. Analgesic indices, physiological, hematological, and biochemical parameters were compared both for differences within and between treatments using repeated measures ANOVA while data for ataxia and sedation were analyzed using Friedman's test. All statistical analysis was performed using an in Vivo Stat software version 4.4.0 and a value of $p < 0.05$ was considered significant.

RESULTS

In the perineal region, medetomidine and lidocaine - xylazine treatment groups produced a significantly earlier onset of analgesia ($p = 0.001$ and 0.039, respectively) than the group treated with xylazine, lidocaine and lidocaine-medetomidine **(Fig.1B).** In the pelvic-abdominal region, the onset of analgesia in the medetomidine treatment group produced a significantly earlier onset of analgesia ($p = 0.001$, 0.006 and 0.015, respectively) than in the xylazine, lidocaine, and lidocaine-medetomidine treatment groups **(Fig.1C).** Furthermore, in the thoracic region, the medetomidine treatment group produced a significantly earlier onset of analgesia ($p = 0.0063$) than the xylazine treatment group, while the lidocaine, lidocaine-xylazine, and lidocaine-medetomidine treatment groups did not produce analgesia in this region **(Fig.1D).** Additionally, medetomidine treatment demonstrated a significant ($P < 0.001$) increase in the duration of analgesia compared to lidocaine, xylazine, lidocaine-xylazine and lidocaine-medetomidine in all the regions observed **(Fig.1).**

Fig.1: Mean ± SD of onset of analgesia following



epidural injection of lidocaine, xylazine, medetomidine, lidocaine-xylazine and lidocaine-medetomidine in Uda sheep :(A) upper hindlimb, (B) perineal region, (C) pelvic and abdominal region (D) thoracic region. Columns: relative frequency plus SD (n = 6). *p <0.05, **p < 0.01, and ***p ≤ 0.001.XYL= xylazine, LID = lidocaine, MED = medetomidine

Furthermore, following administration of lidocaine, lidocaine - xylazine, and lidocaine – medetomidine in Uda sheep, there was severe incoordination of the hind limb, which started 5–10 minutes post-treatment and was scored 3. Sheep in the xylazine and medetomidine treatment groups were able to stand post-injection. While walking, they showed mild ataxia throughout the period of observation and scored 1. The ataxia median scores {median (lower-upper limit)} in the lidocaine, lidocaine – xylazine and lidocaine-medetomidine treatment groups were statistically significant compared to the medetomidine treatment group ($p = 0.006$) and the xylazine treatment group ($p = 0.006$) **(Table 2).**

Table 2: Ataxia in Uda sheep after lumbosacral epidural injections of lidocaine, xylazine, medetomidine,

lidocaine - xylazine, and lidocaine - medetomidine combinations.

Group	Median scores (Lower – Upper limit)	p value
Lidocaine (2.86mg/kg)	3.00 (0.00-3.00) [a]	0.0001
Xylazine (0.05mg/kg)	1.00 (0.00-1.00) [b]	
Medetomidine (20 µg/kg)	1.00 (0.00-1.00) [b]	
Lidocaine + xylazine (2.15mg/kg + 0.0125mg/kg)	3.00 (0.00-3.00) [a]	
Lidocaine + medetomidine (2.15mg/kg + 5 µg/kg)	3.00 (0.00-3.00) [a]	

[a, b,] Median (Lower – Upper limit) with different superscript letters in the same column are significantly different at $p < 0.05$.

Various degrees of sedation, ranging from mild to moderate, were observed following the administration of treatments. The animals were standing but appeared tired, indicating a mild to moderate degree of sedation until the end of the observation. Mild sedation was observed 10–20 minutes post-treatment and was scored 1; sedation progressed to moderate after 20–90 minutes post-treatment and was scored 2; sedation lessened to mild at 120–240 minutes post-treatment and was scored 1. Mild sedation was observed in the lidocaine-xylazine and lidocaine-medetomidine treatment groups, although all the animals were recumbent and so were scored 1. Xylazine and medetomidine treatment groups produced a significant increase in sedation compared to lidocaine, lidocaine-xylazine, and lidocaine-medetomidine treatment groups ($P < 0.05$) **(Table 3).**

Table 3: Sedative effect of lidocaine, xylazine, medetomidine, lidocaine + xylazine, and lidocaine + medetomidine combinations administered epidurally in Uda sheep.

Group	Median scores (Lower – Upper limit)	P value
Lidocaine (2.86mg/kg	0.00 (0.00-0.00)[a]	0.003
Xylazine (0.05mg/kg)	1.00 (1.00- 2.00)[b]	
Medetomidine (20 µg/kg)	1.00 (1.00 – 2.00)[b]	
Lidocaine + xylazine (2.15mg/kg + l 0.0125mg/kg)	0.00 (0.00 – 1.00)[a]	
Lidocaine + medetomidine (2.15mg/kg + 5 µg/kg)	0.00 (0.00 – 1.00)[a]	

As shown in **Table 4**, epidural administration of lidocaine, xylazine, lidocaine – xylazine and lidocaine – medetomidine treatments resulted in a significant decline in PCV and haemoglobin Concentration values at after onset of analgesia when compared to medetomidine treatment group ($P < 0.05$). The medetomidine and lidocaine treatment groups resulted in a significant increase in WBC value at 24 hours post-administration when compared to xylazine treatment groups ($p < 0.05$).

Table 4: Effects of epidural injection of lidocaine, xylazine, medetomidine, lidocaine-xylazine and lidocaine – medetomidine on haematological parameters in Uda sheep:

Parameters	Group	Baseline	After onset	After 24h
PCV (%)	Lidocaine	27.60 ± 5.64	25.20 ± 3.83[ab]*	27.10 ± 4.07
	Xylazine	26.40 ± 3.02	23.80 ± 2.90[b]	29.60 ± 5.07
	Medetomidine	32.90 ± 8.04	33.90 ± 8.17[c]	29.22 ± 3.76
	Lid - Xyl	25.48 ± 2.47	24.50 ± 3.52[abde]	26.55 ± 2.57
	Lid – Med	26.50 ± 1.90	24.80 ± 1.50[abde]	26.90 ± 0.94
HGB (g/dl)	Lidocaine	9.10 ± 1.86	8.40 ± 1.26[ab]*	9.00 ± 1.42
	Xylazine	8.80 ± 1.00	7.90 ± 0.97[b]	9.90 ± 1.69
	Medetomidine	10.69 ± 2.68	11.30 ± 2.73[c]	9.78 ± 1.20
	Lid - Xyl	8.48 ± 0.81	8.16 ± 1.17[abde]	8.83 ± 0.85
	Lid – Med	8.80 ± 0.62	8.30 ± 0.48[abde]	8.90 ± 0.33
RBC x 10^6/ml	Lidocaine	3.50 ± 0.82	3.30 ± 2.63	3.70 ± 0.97
	Xylazine	3.60 ± 0.68	3.20 ± 0.50	4.30 ± 0.94
	Medetomidine	4.64 ± 1.10	4.16 ± 0.30	4.18 ± 0.63
	Lid - Xyl	3.66 ± 0.25	3.29 ± 0.63	3.78 ± 0.46
	Lid – Med	3.50 ± 0.40	3.50 ± 0.40	3.70 ± 0.28
WBC x 10^3/µL	Lidocaine	16.60 ± 9.02	14.40 ± 6.78	19.70 ± 7.38[ac]*
	Xylazine	19.00 ± 7.87	15.80 ± 5.93	13.38 ± 3.56[b]*
	Medetomidine	11.90 ± 2.40	12.83 ± 4.13	19.80 ± 4.52[c]*
	Lid - Xyl	14.10 ± 2.67	11.00 ± 4.28	15.40 ± 6.55[bde]
	Lid – Med	13.10 ± 2.87	13.10 ± 3.13	14.40 ± 2.61[bde]

All treatments had no significant effect on creatinine, but lidocaine and lidocaine-xylazine treatment groups showed significantly higher blood urea nitrogen levels compared to medetomidine and xylazine treatment groups at 24 hours post-administration (P< 0.05). For liver enzyme activity, all treatments had no effect on alanine aminotransferase enzyme activity (ALT) and aspartate transaminase enzyme activity (AST) at all time points, and alkaline phosphate enzyme activity (ALP) was significantly increased in the xylazine treatment group when compared to lidocaine, medetomidine, lidocaine - xylazine and lidocaine-medetomidine at 24 hours post-administration (P< 0.05) **(Table 5).**

Table 5: Effects of epidural injection of lidocaine, xylazine, medetomidine, lidocaine-xylazine and lidocaine – medetomidine on liver and kidney function in Uda sheep.

Parameters	Group	Baseline	After onset	After 24 h
BUN *mg/dl*	Lidocaine	5.50 ± 0.90	5.80 ± 0.90	5.90 ± 0.72 [a]
	Xylazine	5.30 ± 1.21	5.60 ± 0.72	4.50 ± 0.42[be]
	Medetomidine	4.01 ± 0.51	4.83 ± 0.29	3.13 ± 0.68[ce]
	Lid - Xyl	5.51 ± 0.87	5.95 ± 0.76	5.90 ± 0.43[ade]
	Lid – Med	5.30 ± 0.96	5.50 ± 0.89	5.50 ± 0.70[ade]
CREATININE *mg/dl*	Lidocaine	0.90 ± 0.08	0.90 ± 0.15	0.90 ± 0.10
	Xylazine	1.10 ± 0.15	0.90 ± 0.14	0.80 ± 0.08
	Medetomidine	0.87 ± 0.05	0.83 ± 0.16	0.80 ± 0.94
	Lid - Xyl	0.86 ± 0.81	0.98 ± 0.09	0.88 ± 0.09
	Lid – Med	0.87 ± 0.08	0.97 ± 0.08	0.86 ± 0.08
ALT (IU/L)	Lidocaine	7.80 ± 2.04	9.70 ± 2.33	8.30 ± 1.97
	Xylazine	5.70 ± 3.20	8.35 ± 1.50	6.70 ± 2.07
	Medetomidine	7.66 ± 1.36	7.33 ± 2.42	6.66 ± 3.00
	Lid - Xyl	8.50 ± 2.66	10.32 ±0.81	8.33 ± 1.96
	Lid – Med	7.30 ± 1.00	9.00 ± 2.10	7.00 ± 2.10
AST (IU/L)	Lidocaine	7.00 ± 2.10	7.00 ± 1.67	6.30 ± 1.10
	Xylazine	8.30 ± 1.50	7.80 ± 3.37	7.00 ± 2.76
	Medetomidine	5.00 ± 1.09	7.66 ± 1.50*	6.33 ± 1.96
	Lid - Xyl	7.33 ± 2.06	6.90 ± 2.42	5.80 ± 1.63
	Lid – Med	6.70 ± 2.40	7.70 ± 1.50	6.30 ± 1.80
ALP (IU/L)	Lidocaine	62.70 ± 8.29	66.30 ± 4.80	63.80 ± 5.23[a]
	Xylazine	67.50 ± 4.64	70.50 ± 9.75	74.50 ± 8.43[b]
	Medetomidine	65.67 ± 6.65	61.33 ± 4.27	64.00 ± 6.60[acde]
	Lid - Xyl	61.33 ± 7.78	65.83 ± 4.44	63.50 ± 4.03[acde]
	Lid – Med	64.50 ± 6.80	66.70 ± 5.80	61.20 ± 4.60[acde]

*difference between baseline value and the corresponding time-point within the group (P< 0.05).
[a-e] within column without a common superscript differs significantly (P < 0.05). Data were expressed as mean ± SD (n=6).

DISCUSSION

This study was undertaken to compare the analgesic effects and hemato-biochemical changes produced by the administration of lidocaine, xylazine, and medetomidine alone and their combinations with lidocaine in the epidural space of Uda sheep. This study clearly demonstrated that medetomidine epidural administration in lumbosacral space could be useful clinically to provide rapid onset, prolonged and safe epidural analgesia, which is required for long-duration surgical and obstetrical operations in standing sheep. The mean onset of analgesia in the perineal and pelvic-abdominal and thoracic regions was faster in the medetomidine treatment group (6–8 min) than in the lidocaine, lidocaine – xylazine and lidocaine-medetomidine treatment groups and much faster than xylazine treatment group. The differences in the mean onset of analgesia could be due to their different mechanisms of action or the time taken for these agents to reach their site of action from the epidural space.

The result of this study agreed with that of **Kinjavdekar *et al*., (2000)** who reported a faster onset

of analgesia for medetomidine when compared to xylazine administered epidurally in goats. The mean duration of analgesia in the upper hindlimb, perineal and pelvic-abdominal areas was longer in the medetomidine treatment group (190-230 min) than in the lidocaine, lidocaine-xylazine, and lidocaine-medetomidine treatment groups. The prolonged analgesia observed in medetomidine treatment could be due to its high potency, greater selectivity and specificity to α 2-adrenoceptors **(Sinclair, 2003).**

In addition to this, medetomidine activates the peripheral sub α_{2A}- adrenoceptor (which regulates the peripheral vasoconstrictive effects) to produce a vasoconstrictive effect at the site of administration. This could account for the increased duration of analgesia observed in this study. This is in line with **Singh *et al*., (2005)** who reported that epidural administration of medetomidine produced prolonged durations of analgesia when compared to bupivacaine and xylazine in buffaloes. The short duration of lidocaine observed in this study could be due to the local vasodilatory effect of the drug at the epidural site of administration, which facilitates its systemic absorption, thereby shortening its duration of action.

The results of this study agreed with those of **Aminkov and Hubenov (1995); Grubb *et al*., (2002); and Derossi *et al*., (2005)** who reported a short duration of analgesia in lidocaine group when compared to lidocaine-xylazine combination administered epidurally in sheep, cattle, and goats, respectively. This disagreed with **Rostami *et al*., (2012)** who reported a non-significant difference between lidocaine and lidocaine-xylazine combinations in fat-tailed sheep. The author may attribute the lack of significance to the low dose used in the study. Furthermore, the duration of analgesia was also prolonged in lidocaine-xylazine and xylazine treatment groups when compared to lidocaine and lidocaine-medetomidine. It has been shown that local anaesthetic when combined with alpha-2 agonists increase the duration of analgesia more than using either of the drugs alone following epidural administration **(Zayed *et al*., 2020).** In this study, the combination of lidocaine and medetomidine does not also provide much duration of analgesia when compared to lidocaine, which could be due to the small dose (5 μg/kg) used in this study or could be due to the incompatibility of lidocaine – medetomidine combination in the same syringe as previously reported with detomidine **(Zayed *et al*., 2020).**

Duration of analgesia in the thoracic region was only observed in the medetomidine and xylazine treatment group. In this present study medetomidine and xylazine produced a qualitatively equal degree of analgesia in the upper hindlimb, perineal, pelvic and abdominal, and thoracic regions. It has been reported that cranial absorption of these agents from epidural space induced general inhibition of the sympathetic nervous system activity reflexes within the thoracic region **(Sinclair, 2003).** In this study also medetomidine treatment produced prolonged duration of analgesia than the xylazine treatment group. The prolonged analgesia observed in the medetomidine treatment group could be due to high potency, more selectivity, and specificity to α2- adrenoceptors than xylazine (α2/ α1 = 1620:1 and 160:1, respectively). The result of this study is in line with **Kinjavdekar *et al*., (2000)** and **Singh *et al*., (2005)** who reported prolonged duration of medetomidine when compared to xylazine administered epidurally in goats and buffaloes respectively.

The mean standing time of lidocaine, lidocaine – xylazine and lidocaine - medetomidine treatment groups was prolonged compared to medetomidine and xylazine treatment groups. Sternal recumbency can be anticipated following epidural administration of lidocaine and lidocaine-α2-adrenoceptor combinations because lidocaine indiscriminately blocks both sensory and motor functions. The result of this study disagreed with those of **Umar and Gapsiso (2008)** who reported prolonged standing time following lumbosacral administration of 1 mg/kg of xylazine in goats. The discrepancy in the duration of standing time in the xylazine treatment group could be due to specific effects or the high dose of xylazine used in their study.

In all the subjects, severe incoordination of the hindlimb leading to recumbency was observed in lidocaine, lidocaine – xylazine and lidocaine-medetomidine treatment groups, while mild coordination of the hindlimb was observed in all the subjects in xylazine and medetomidine treatment groups. Ataxia leading to recumbency can be anticipated following epidural administration of lidocaine and lidocaine – α2- adrenoceptors combinations because lidocaine blocks both sensory and motor functions. The result of this study agreed with **Derossi *et al*., (2005) and Rostami *et al*., (2012)** who reported severe ataxia and recumbency following epidural administration of lidocaine and lidocaine-xylazine treatment in goats and sheep, respectively, while it disagreed with Zayed *et al*. (2020) who reported no ataxia following epidural administration of lidocaine-detomidine in goats. The mild ataxia recorded in the xylazine and medetomidine treatment groups could likely be due to the central sedative effect of α2 agonists following systemic absorption. The result of this study agreed with that of **Kinjavdekar *et al*., (2000)** who reported mild ataxia following epidural administration of xylazine and medetomidine in goats.

The mild to moderate sedation observed in xylazine, medetomidine, lidocaine-xylazine and lidocaine-medetomidine treatment groups could be due to the systemic absorption of xylazine and medetomidine from the epidural space to the sheep brain stem, where it binds with alpha-2 subreceptors, which are responsible for causing sedation in sheep **(Sinclair, 2003).** The result of this study agreed with **Kinjavdekar *et al*., (2000) and Singh *et al*., (2005)** who reported that epidural administration of xylazine and medetomidine produced mild to moderate sedation in goats and buffaloes, respectively. This is also in line with **Rostami *et al*., (2012)** who reported similar results following epidural administration of xylazine and lidocaine-xylazine in sheep. The present study disagreed with **Grubb *et al*., (2002)** who reported that horses do not generally become sedated after an epidural injection of xylazine.

The epidural administration of lidocaine, xylazine, lidocaine-xylazine, and lidocaine-medetomidine in this study resulted in a decrease in PCV and HGB values when compared to the medetomidine treatment group after the onset of analgesia. The decrease could be due to the shifting of fluid from the extravascular compartment to the intravascular compartment to maintain cardiac output **(Zayed *et al*., 2020)** and might also be due to the pooling of circulatory blood cells in the spleen secondary to decreased sympathetic activity **(Sharda *et al*., 2008).** White blood cells increased in the lidocaine and medetomidine treatment groups when compared to baseline values. The increase in WBC might have been caused by stress-induced leucocytosis. This coincides with **Moulvi *et al*., (2011)** and **Kayode (2017)** who reported an increase in the value of WBC following the administration of lidocaine in calves and goats, respectively.

Blood urea nitrogen (BUN) values increased in the group of lidocaine and lidocaine-medetomidine treatment groups after 24 hours post-administration when compared to xylazine and medetomidine treatment groups. The increase may be attributed to a temporary inhibitory effect of the drug on renal blood flow, which might have caused a rise in BUN **(Kinjavdekar *et al*., 2000; V. Singh *et al*., 2005; Moulvi *et al*., 2011).** However, it is difficult to attribute this to possible renal damage as BUN values were within normal limits. This coincides with **Zayed *et al*. (2020)** who reported a similar result following epidural administration of lidocaine in goats.

Alkaline phosphate (ALP) values increased in the xylazine treatment group, while aspartate transaminase (AST) values in the medetomidine treatment group increased when compared to lidocaine, lidocaine-xylazine and lidocaine-medetomidine groups at 24 hours post-administration. The increase in the ALP and AST values may be due to some alteration in cell membrane permeability, which may permit this enzyme to leak from the cells with intact membranes **(Singh *et al*., 2005).** The result of this study is in line with **Moulvi *et al*., (2011)** who reported similar results after epidural administration of xylazine in calves.

CONCLUSION

In conclusion, this study shows that medetomidine administered epidurally at a dose rate of 20µg/kg was the most effective agent with rapid onset of analgesia (6–8 min), prolonged duration of analgesia (190-230 min), shorter standing time (less than a minute), followed by lidocaine-xylazine combination (Lid 2.15 mg/kg - Xyl 0.0125 mg/kg) and xylazine (0.05 mg/kg) that produced delayed onset of analgesia similar to lidocaine but provided safe and prolonged analgesia of 100–130 minutes and 130–140 minutes, respectively. A surgical procedure could be done with medetomidine (20 µg/kg) and xylazine (0.05 µg/kg) while the sheep remained in a standing position. Medetomidine specifically did not affect hemo-biochemical parameters except for WBC and AST. The haematological and biochemical alterations produced by medetomidine, xylazine and lidocaine-xylazine were transient in nature and returned to normal levels as the effects of these drugs weaned off.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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