Iranian Veterinary Surgery Association

IRANIAN JOURNAL OF VETERINARY SURGERY

Journal homepage: www.ivsajournals.com

ORIGINAL ARTICLE

Comparison the Effect of Lidocaine in Combination to Meloxicam and/or Metamizole Sodium Epidurally on Analgesic Parameters, and Health Status of Holstein Cattle

Khosro Safari-Nikroo[1], Abbas Raisi[1*], Amir Zakian[1], Ahmad Reza Mohamadnia[2]

[1]*Department of Clinical Sciences, Faculty of Veterinary Medicine, Lorestan University, Khorramabad, Iran.*

[2]*Department of Clinical Sciences, Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, Iran.*

Received: 18 August 2020
Accepted: 21 September 2020
Online: 21 September 2020

Keywords:

Epidural analgesia;

Electrocardiography;

Lidocaine;

Meloxicam/metamizole;

Cow.

Abstract

Objective- This practice performed to compare the quality of analgesia, hematological parameters, and prevalence of cardiac dysrhythmias following epidural administration of lidocaine, lidocaine-meloxicam, and lidocaine-metamizole sodium in cows.

Animals- Fifteen adult Holstein cows aged 3-5 years were assigned into three equal groups.

Design- Each cow received the lidocaine (0.22 mg/kg), lidocaine-meloxicam (0.11 mg/kg–0.25 mg/kg) or lidocaine-metamizole sodium (0.11 mg/kg-4 mg/kg) randomly via epidural injection into the first intercoccygeal space.

Procedures- Analgesia onset and duration were recorded. Heart rate, respiratory rate, rectal temperature, and ruminal motility were also recorded at 0, 5, 15, 30, 45, 60, 90, and 120 minutes, and electrocardiograms were also recorded at 0, 60, and 120 minutes. Blood samples were collected through the caudal vein at 0, 30, 60, 90, and 120 minutes. Detection of arrhythmias was done by checking 60 seconds of each electrocardiogram.

Results- analgesia onset in lidocaine-metamizole treatment was significantly longer than that of the other groups ($p < 0.05$). Also, the duration of analgesia was significantly longer in lidocaine treatment compared to other experimental groups ($p < 0.05$). There were no significant differences among heart rate, respiratory rate, rectal temperature, and ruminal motility between experimental groups ($p > 0.05$). Hematological parameters changes were not significantly different and all of the detected cardiac arrhythmias were physiologic among treatments ($p > 0.05$).

Conclusions and Clinical Relevance- Aforementioned dosages could be used in cows without any clinical, cardiac, and hematological side effects. Lidocaine analgesia was reliable; however, the authors were not sure about adequate analgesia resulted after injection the half-dose of meloxicam and Metamizole in combination with lidocaine therefore, further studies should be done.

* Correspondence to: Abbas Raisi, Department of Clinical Sciences, Faculty of Veterinary Medicine, Lorestan University, Khorramabad, Iran. E-mail: raisi.a@lu.ac.ir

DOI: 10.30500/ivsa.2020.244439.1222

1. Introduction

General anesthesia in ruminants (cattle, sheep, goats, and camels) is not considered as a method of choice due to the dangers and risks of aspiration ruminal contents or saliva.[1,2] Different techniques of anesthesia (local, regional, or epidural) may be used in many situations with fewer risks and are more effective than general anesthesia. Most of the surgical operations can be performed with safety and minimum pain in ruminants using a combination of physical restraint, sedation, and aforementioned methods. These kinds of analgesia also provide advantages over general anesthesia, including lower risk of toxicity, recumbency complications (bloat, regurgitation), and the requirement of a complex equipment.[3]

Caudal epidural analgesia is the most common anesthetic technique in small and large ruminants to allow parturition and surgery in tail, anus, rectum, bladder, urethra, and perineal region.[1,4] It is also utilized for controlling rectum tenesmus,[5] the performance of simple embryotomies, and inhibition of straining to facilitate manipulative correction of fetus malpositions and reduction of the prolapsed uterus.[6] Lower used volume of anesthetic agents besides the ability to do standing surgeries are the most important advantages of caudal epidural anesthesia in cattle.[7] However, by blocking motor and sensory nerves it may result in severe ataxia and recumbency, which is a disadvantage in standing surgeries.[6]

Lidocaine is one of the frequent local anesthetic drugs used in epidural anesthesia, however, it has a comparatively short duration and may require several administrations.[8] Furthermore, It is one of the class 1b antiarrhythmic agents that can be effective in suppressing ventricular arrhythmias like other class1 drugs.[9] Meloxicam as a non-steroidal anti-inflammatory drug (NSAID) can modulate pain and present analgesia via central and peripheral actions through selective inhibition of cyclooxygenase (COX-2). Epidural administration of meloxicam has been studied, and its effectiveness has been shown.[10] NSAIDs are used alternatively to opioids since they have less adverse effects such as respiratory depression and vomiting, which are frequently associated with opioid utilization. One of the main advantages of the epidurally administered NSAID is the discreet action in the gastric, renal, and hepatic systems in addition to platelet aggregation and fewer obvious side effects.[11] Metamizole sodium (or dipyrone) is a popular analgesic, non-opioid drug, commonly used in human and veterinary medicine. In some cases, metamizole is still wrongly classified as an NSAID drug. The mechanism involved in its analgesic effect is complex and most probably comes from both action of COX-3 and the impact on opioidergic and cannabinoid systems.[12] Despite the widespread administration of metamizole in veterinary practice as an analgesic and antinociceptive medication, no study regarding epidural usage of metamizole in animals was published. Hematologic disorders have long been a potential risk of modern pharmacotherapy. The most common drug-induced hematologic disorders include agranulocytosis, thrombocytopenia, and methemoglobinemia which sometimes associated with consistent use of lidocaine, other local anesthetics or metamizole sodium and NSAIDs.[12-15]

This study was done to evaluate the effectiveness of the administration of meloxicam or metamizole sodium in combination with lidocaine in order to compare analgesic, hematologic parameters to lidocaine when administrated alone in caudal epidural space of cattle. The hypothesis was that the addition of meloxicam or metamizole sodium could reduce the onset and prolong the duration of analgesia, and there should be a decrease in the number of cardiac arrhythmias in these combination groups (which is the result of adding an arrhythmic drug like lidocaine) without the hematologic and clinical side effects.

2. Materials and Methods

Animals

Fifteen adult non-pregnant Holstein cows were randomly selected from the research farm of the Faculty of

Agriculture, Lorestan University. Before any procedure cows underwent examinations, and the health status of the animals was approved by recording heart rate (HR), respiratory rate (f_R), rectal temperature (RT), and physical conditions. The last food meal was withdrawn before each experiment. This study was confirmed by the animal ethics committee of Lorestan University (LU.ACRA.2018.11).

Medications

All fifteen cows were randomly divided into 3 groups of 5 animals. Group LID received 0.22 mg/kg (5.5 ml/500 kg) lidocaine HCl 2% without epinephrine (Vetacaine 20 mg/ml, Aburaihan Pharmaceutical Co., Iran), Group LID-MLX received 0.11 mg/kg (2.75 mL/500 kg) lidocaine 2% and 0.25 mg/kg (6.25 ml/500 kg) meloxicam (Meloxivet 20 mg/ml, Razak Laboratories Co., Iran), and group LID-MTZ received 0.11 mg/kg lidocaine 2% and 4 mg/kg (6.5 ml/500 kg) metamizole sodium (Analgine 300 mg/ml, Hanvet Pharmaceutical and Veterinary Material J.S.C., Vietnam). The initial volume of each treatment was calculated based on the dosage mentioned above, and the final volume was reached to 10 ml [7] in all treatments using sterile injectable 0.9% normal saline solution.

Experimental Design

The animals were restrained in standing position in the stanchion 15-20 minutes before the study. The HR was measured with a stethoscope, f_R by observation of chest movements in a 60 sec period, RT by a mercury thermometer, and rumen motility (RM) with stethoscope on left flank over 2 minutes. HR, f_R, and RT were recorded for each animal in checklists for each medication group at 0, 5, 15, 30, 45, 60, 90, and 120 minutes after injection of the medication. Electrocardiogram (ECG) was recorded in 0 (baseline), 60, and 120 minutes (Kenz Cardico 302, Suzuken, Japan). Blood samples (EDTA/k2 test tube, Tajhiz Gostar, Isfahan, Iran) were collected from the coccygeal vein at 0, 30, 60, 90, and 120 minutes for measuring routine hematology parameters [red blood cells (RBC), hemoglobin (Hb), hematocrit (HCT) and white blood cells (WBC)] by automated hematology analyzer (Celltac Alpha VET MEK-6450, Japan).

The first intercoccygeal space was identified by finger palpation of vertebral articulations in tail by raising and lowering. The hair of the area was clipped by an automatic machine clipper and scrubbed aseptically using povidone-iodine (10% Betadine, Nasr Co, Iran) and area of coccygeal vein swiped with antiseptic gauze to remove the superficial dirt. Proper needle (18-gauge, 3.8 cm) placement was determined by loss of resistance and ease of injection of a small volume (2-3 ml) of air.[16] The bevel of the needle was pointed in a cranial direction with approximately 45° to the skin surface centered on the dorsal midline and drugs were slowly injected within 20 seconds.

Time to onset, time to tail paralysis, the duration of anesthesia, and the score of ataxia were recorded. Time from the injection to loss of sensation in the perineal region was considered as the time of onset of anesthesia. Tail paralysis after epidural injection was identified by flaccidity and inability of tail movement. The time between onset and reappearance of pain response in the perineal region was considered as the duration of anesthesia. Lack of response to pressure from the hemostat clamp (closed to the first ratchet) applied in the perineal area was defined as an anesthetized area. The response was measured each minute until no reaction occurred, and then at 5 minutes intervals until getting a response (movement associated with hemostat pressure)[4] by the observer that was not aware of the given drugs. All epidural injections were performed by one person who was blind to treatments. Electrocardiographs were collected and kept in a dry Ziploc plastic for further reading of heart electrical activity and detection of arrhythmias. Observation of each digitally scanned ECG for detection of arrhythmias was done by checking 60 seconds of each electrocardiogram. Scores of ataxia were observed and determined by walking the cow

out of the stanchion in the 60 and 120 minutes after injection. The ataxia was graded as mild (slight stumbling, easily able to continue walking), moderate (marked stumbling, walking but very ataxic), or severe (falling).[17]

Statistical analysis

Statistical analysis was performed using MedCalc Software (version 14.8.1, Ostend, Belgium) and Analyse-it software for Windows (version 4.80.8, Leeds, UK). The normal distribution of data was evaluated using the Shapiro-Wilk test. Normal data distributions were expressed as mean ± standard deviation (SD) and non-normal data distributions by median and quartile range. HR, f_R, RT, and RM were compared to baseline values using repeated measures analysis of variance (ANOVA) followed by Duncan's test was used to compare treatments. Times to onset and duration of caudal epidural analgesia were compared within each treatment using a paired samples t-test. A one-way repeated measure ANOVA followed by Bonferroni's test was used to compare the onset and duration of caudal epidural analgesia between treatments. A value of $p < 0.05$ was considered significant.

3. Results

Mean ± SD with 95% confidence interval of age, body weight, and body condition score (BCS) of animals were 3.67 ± 0.82 (95% CI: 3.37-4.3) year, 430 ± 27.45 (414.8-445.2) kg, and 3.31 ± 0.176 (3.22-3.4), respectively. There were no significant differences in age, body weight, and BCS between groups ($p > 0.05$). The pH of each medication was measured (lidocaine = 6.10, meloxicam = 8.70, and metamizole sodium = 5.45 using a pH meter (Seven Compact S220, Mettler Toledo, Switzerland) separately and in combination with lidocaine. Other combinations were centrifuged and watched for any precipitate and turbidity. Caudal epidural anesthesia was produced in all cows following the administration of three treatments without a prominent problem during the procedures.

The onset of the analgesia in the LID-MTZ group was significantly longer than the two other groups ($p < 0.05$). The duration of the analgesia in the LID group compared to other groups was significantly higher ($p < 0.05$; Figure 1a). No severe ataxia observed, except that only three cows (60%) in the LID group showed moderate ataxia at 60 min, and in the rest of the animals were mild (Figure 1b).

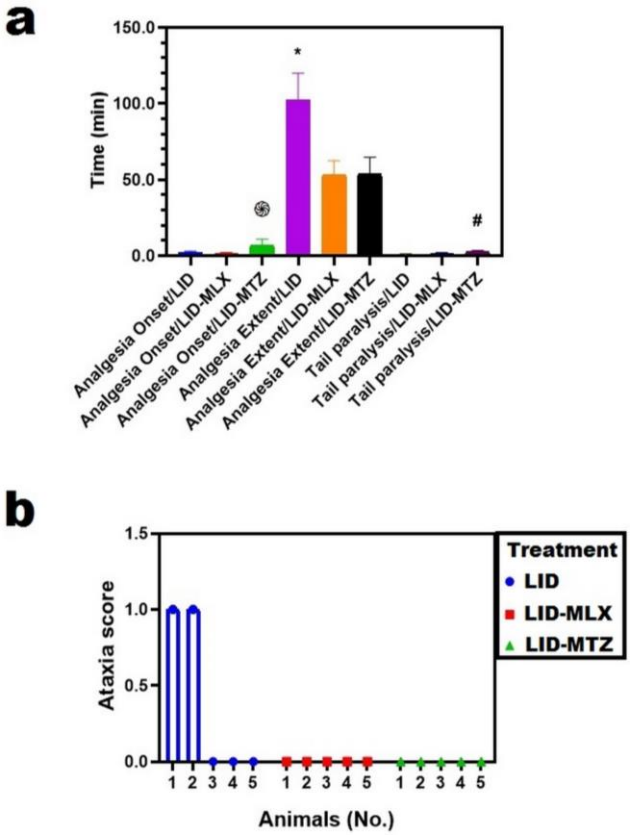

Figure 1. (a), Anesthetic indices, and (b), Ataxia scoring in cattle treated with epidural administration of lidocaine (LID; 0.22 mg/kg), lidocaine (0.11 mg/kg) plus meloxicam (MLX; 0.25 mg/kg) and lidocaine (0.11 mg/kg) plus metamizole sodium (MTZ; 4 mg/kg) for caudal epidural analgesia (mean ± SD; n = 5). Different symbols show significant difference ($p < 0.05$) between treatments.

The difference in HR, f_R, and RT was not significant in all treatment groups ($p > 0.05$). However, the time interaction of RT was significant ($p < 0.05$; Table 1) and RT decreased gradually. No significant difference recorded in hematological parameters within and between groups ($p > 0.05$; Table 2).

Evaluation of electrocardiograms showed that different types of arrhythmias were present (Figure 2 and Table 3).

The heart rate of animals with and without arrhythmia was equal to 72 ± 8 and 79 ± 11, respectively; however, this difference was not statistically significant ($p > 0.05$). Electrocardiogram results of the LID group showed that the intensity of changes in sinus rhythm was increased after lidocaine administration, hence, P-P intervals were increased significantly 120 min after lidocaine administration. In general, the paramorphism and the height of the P (wandering peacemaker) and T waves were increased steadily within the experiment. In addition, the S-T segment in the timeline was associated with changes specially 120 min after lidocaine administration. Electrocardiogram results of LID-MLX treatment showed no change in P-P intervals and sinus arrhythmia was not observed at 60 and 120 min. The results showed that the electrical alternans (EA) and wandering pacemaker which was present at 0 min, remained until 120 minutes. The presence of fewer variations in the position, shape, and intervals of the waves and components were apparently influenced following metamizole sodium administration. Eighty percent of animals showed wandering pacemaker with 27%, 33% and, 20% in the LID, LID-MLX, and LID-MTZ groups, respectively. Sinus arrhythmia was observed in 27% of animals with 13%, 7%, and 7% in the LID, LID-MLX, and LID-MTZ groups, respectively. Sinus tachycardia was observed only in one animal (7%) which was in the LID group. EA were also observed in all cows and it was an expectable event.

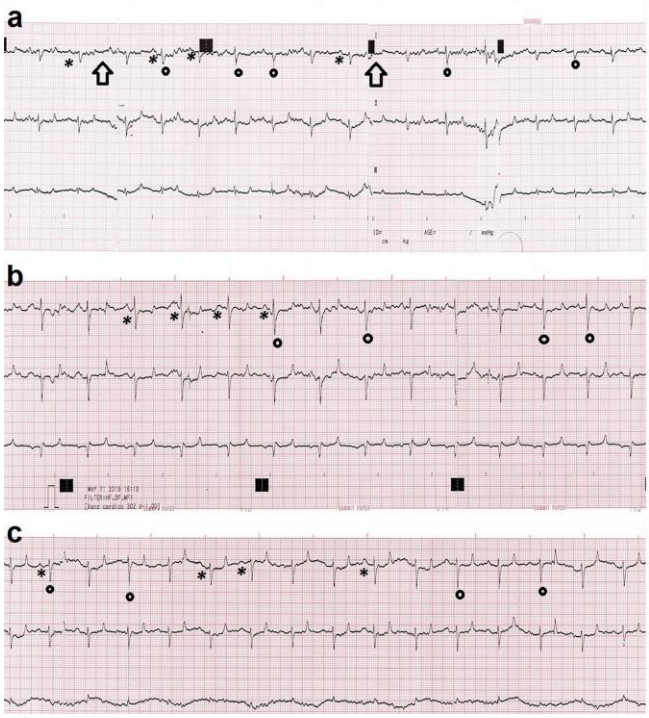

Figure 2. Evaluation of different types of heart arrhythmias in cattle treated with epidural administration of lidocaine (LID; 0.22 mg/kg) (a), lidocaine (0.11 mg/kg) plus meloxicam (MLX; 0.25 mg/kg) (b), and lidocaine (0.11 mg/kg) plus metamizole sodium (MTZ; 4 mg/kg) (c), at 60 minutes after drug consumption. Different symbols show electrical alternans (hollow black circle), wandering pace maker (asterisk), and sinus arrhythmia (arrow) in studied Holstein cows. (Base apex lead, 25 mm sec-1 of 10 mm = 10 mV)

Table 1. Vital sings in cattle treated with epidural administration of lidocaine, lidocaine–meloxicam, and lidocaine–metamizole sodium (mean ± SD; n = 5).

Variable	Group	0 min	5 min	15 min	30 min	45 min	60 min	90 min	120 min
HR (beats/min)	LID	74.8±3.63	75.8±3.19	77.0±9.05	73.6±4.33	70.6±4.67	76.8±7.56	71.4±7.20	72.8±4.38
	LID-MLX	74.4±6.07	74.4±4.56	76.8±3.35	74.2±7.29	74.4±5.90	74.4±3.58	74.2±1.79	76.0±6.32
	LID-MTZ	74.5±4.43	73.0±5.03	72.0±7.30	76.0±5.66	74.0±6.93	74.0±5.16	74.5±6.40	76.5±7.37
f_R (breathes/min)	LID	37.4±9.94	32.8±7.19	30.0±7.21	32.8±5.93	33.4±10.11	36.8±14.04	32.6±5.64	35.4±9.85
	LID-MLX	43.2±8.67	40.8±9.96	36.0±14.70	39.2±8.20	37.6±5.37	34.8±4.38	34.8±4.38	36.8±5.93
	LID-MTZ	43.5±4.72	46.75±2.75	43.5±11.82	43.5±11.12	40.5±6.61	38.5±5.97	38.5±5.00	41.5±9.83
RT* (°C)	LID	39.50±0.58	39.28±0.40	39.32±0.53	39.26±0.61	39.18±0.58	39.12±0.38	39.10±0.46	39.06±0.51
	LID-MLX	38.92±0.22	38.94±0.11	38.72±0.27	38.86±0.26	38.84±0.15	38.86±0.21	39.04±0.23	39.96±0.23
	LID-MTZ	39.00±0.22	39.07±0.22	39.15±0.25	39.17±0.24	39.12±0.19	39.50±0.25	39.00±0.14	39.00±0.14

* Significant difference of time interaction in $p < 0.05$.

Table 2. Blood parameters in cattle treated with epidural administration of lidocaine, lidocaine–meloxicam, and Lidocaine–metamizole sodium (mean ± SD; n = 5).

Variable	Group	0 min	30 min	60 min	90 min	120 min
RBCs (10^6/mm^3)	LID	5.50±0.62	5.48±0.66	5.32±0.36	5.32±0.45	5.67±0.87
	LID-MLX	6.07±0.74	5.65±0.80	5.62±0.63	5.77±0.78	6.09±0.82
	LID-MTZ	5.89±1.06	5.72±0.76	5.77±0.76	5.77±0.72	5.65±0.77
Hb (gr/dL)	LID	6.68±0.16	7.14±0.01	7.16±0.27	6.56±0.32	6.98±0.28
	LID-MLX	7.72±2.11	7.26±1.93	8.14±2.85	7.16±1.99	7.92±2.05
	LID-MTZ	8.90±1.13	8.68±1.68	8.50±2.01	7.58±3.42	10.06±0.70
PCV (%)	LID	8.74±0.73	8.70±80	8.46±0.37	8.44±0.59	8.04±1.15
	LID-MLX	8.96±0.65	8.90±0.89	8.46±0.27	8.64±0.50	9.10±1.07
	LID-MTZ	9.28±0.90	8.96±0.49	9.06±0.49	8.84±0.46	8.92±0.50
WBCs (10^3/mm)	LID	6.68±0.16	7.14±0.01	7.16±0.27	6.56±0.32	6.98±0.28
	LID-MLX	7.72±2.11	7.26±1.93	8.14±2.85	7.16±1.99	7.92±2.05
	LID-MTZ	8.90±1.13	8.68±1.68	8.50±2.01	7.58±3.42	10.06±0.70

Table 3. The definitive and relative frequency distribution of different types of heart arrhythmias in cattle treated with epidural administration of lidocaine, lidocaine– meloxicam, and lidocaine–metamizole sodium (n = 5)

Group	Wandering pacemaker	Sinus arrhythmias	Sinus tachycardia	Electrical alternans	Total
LID					
0 min	8 (33.33%)	6 (25%)	2 (7.69%)	8 (33.33%)	26 (24%)
60 min	6 (33%)	3 (18%)	1 (5%)	8 (44%)	18 (18%)
120 min	4 (31%)	3 (23%)	-	6 (46%)	13 (13%)
LID-MLX					
0 min	6 (35%)	2 (12%)	1 (6%)	8 (47%)	17 (17%)
60 min	4 (40%	-	-	6 (60%)	10 (10%)
120 min	5 (50%)	-	-	5 (50%	10 (10%)
LID-MTZ					
0 min	6 (50%)	-	-	6 (50%)	12 (12%)
60 min	8 (61%)	1 (8%)	-	4 (31%)	13 (13%)
120 min	8 (57%)	2 (14%)	-	4 (29%)	14 (14%)

4. Discussion

Epidural anesthesia is a simple, inexpensive, and effective way to prevent or control pain in the anus, vulva, perineum, tail, caudal udders, scrotal region, and upper pelvic limb surgeries.[18] There are several studies on caudal epidural anesthesia that investigated the lidocaine or other local anesthetics alone[5,19,20] and/or in combination with other agents[1,2,21,22] in cattle and other ruminants.[1,4,23,24]

The onset of analgesia in the current study was fast and results were in agreement with other studies which used bupivacaine in cow.[5,20] However, the onset of analgesia was slower in tramadol/lidocaine in cattle[6] in comparison with our current results that may be due to higher lipid solubility and more tissue affinity of lidocaine in comparison with tramadol which is more water-soluble.[25,26] The rate of administration may affect the onset of analgesia. The present study showed that lidocaine injection caused intermediate-acting duration analgesia, which supported the study of lumbosacral injection of lidocaine 2% mixture that provided sufficient analgesia to permit umbilical surgery in calves.[27]

In the present study, the duration of analgesia in lidocaine-meloxicam and lidocaine-metamizole was shorter than the

lidocaine group. In contrast, others showed that lidocaine-xylazine in cattle and lidocaine-meloxicam in dogs produced longer duration.[10,17,24] It may be attributed to α-2 adrenergic agonists vasoconstriction and inhibition of local anesthetic agent-induced vasodilation and subsequently reduction in vascular uptake of the anesthetic agents.[28,29] The bovine spinal cord ends in the lumbosacral region and drugs administered in the caudal epidural space are cranially diffused to connect with cord receptors. The decreased concentration of drugs in combinations, normal saline solution, and the lack of vasoconstriction effect may explain the shorter duration of analgesia in the present study. The reason for the duration difference between dog and cattle is unknown, however, anatomical and species differences may explain the phenomenon.[30]

Moreover, meloxicam has 99.4% and two active metabolites of metamizole (4-methyl-amino-antipyrine and 4-aminoantypyrine), have 57.6% and 47.9% of plasma protein binding (PPB) that may cause less distribution of the drugs and besides short half-life of the drug may result in shorter analgesia in two combinations.[31]

Mild and moderate ataxia was observed in the present study. Similar findings reported by others on bucks,[1] cattle,[2] and donkey[32] after injection of lidocaine, probably could be related to sensory and motor fibers blockade.[33] Cardiopulmonary changes were not significant among treatments and it was in agreement with the results of others on cattle, horse, donkey, buffalo calves, and dog.[7,10,32,34-36] The rectal temperature remained consistent among groups. Similar investigations reported the same results in lamb, buck, and cow.[1,4,7]

Decrease and increase in hematological parameters were recorded, however, it was not significant among groups and within the study period. This result was similar to studies on male mice[37] and Albino rats, and that because the permitted therapeutic dose of meloxicam was used in the present study. Those studies showed that the effect of meloxicam was dose-dependent and when administrated with a high dose significant decrease in blood indices was observed.[38] There were different findings in other studies by administering lidocaine and lidocaine-neostigmine in buffalo calves,[39] lidocaine alone or in combination with xylazine in cow calves,[40] xylazine, and xylazine-detomidine in horses,[41] and xylazine and lidocaine in dogs[42] in which hematological parameters were decreased. This decline could be due to the shifting of fluids from the extravascular compartment to the intravascular compartment to compensate normal cardiac output and pooling of blood cells in the reservoir organs like spleen secondary to decrease sympathetic activity.

Although cardiac arrhythmias due to the number of animals per treatment were not obvious it seems that all the arrhythmias in the present study were physiologic and there were no pathological changes. Lidocaine has little effect on atrial arrhythmias, as might be predicted from lack of effect on atrial tissues in normal animals. The drug can, but not always, cause slight slowing of atrial rate in atrial flutter. Lidocaine causes no change or decrease in A-V conduction time and A-V refractoriness which proves the results of the present study. The stress-induced changes after drug injection, manipulation, vagal stimulations, and electrolyte imbalances during the study period may partly justify some changes in heart rhythm at different times. The findings of the present study revealed that mixed drug regimens such as lidocaine with meloxicam or metamizole sodium not only did not have a negative and pathological change in cardiac function but also prevented the occurrence of sinus arrhythmia and severe changes in S-T segment, P-P intervals. It could be concluded that the administration of these combinations could have better effects on cardiovascular function than the administration of lidocaine only.[43-45]

In conclusion, lidocaine alone provided an adequate duration of analgesia which probably enough for most of the reproductive procedures, however, the authors were not sure about adequate analgesia resulted after injection the half-dose of meloxicam and Metamizole in combination with lidocaine, therefore, further studies

should be done. On the other hand, they were safe with no hematological or clinical side effects. One of our limitations was the number of sample size. Another limitation of the present study was the lack of measurement of blood glucose and cortisol concentrations as an indicator of stress in the studied animals. The authors suggest further studies should be done with greater sample size and higher doses of meloxicam or metamizole.

Acknowledgments

This work was supported by the Department of Clinical Sciences, Faculty of Veterinary Medicine, Lorestan University grant number LU-9211501019-2020. We would like to show our appreciation to Dr. Farshid Davoodi for assisting us in the animal trial.

Conflict of Interests

The authors declare no conflict of interest.

References

1. Ragab GA, Fathy MZ. Evaluation of the epidural analgesic effect of nalbuphine, lidocaine and nalbuphine-lidocaine combination in bucks. *Beni-Suef University Journal of Basic and Applied Sciences*, 2018; 7(1): 27-30.
2. Bigham AS, Habibian S, Ghasemian F, Layeghi S. Caudal epidural injection of lidocaine, tramadol, and lidocaine-tramadol for epidural anesthesia in cattle. *Journal of Veterinary Pharmacology and Therapeutics*, 2010; 33(5): 439-443.
3. Edmondson MA. Local, Regional, and spinal anesthesia in ruminants. *Veterinary Clinics of North America: Food Animal Practice*, 2016; 32(3): 535-552.
4. Habibian S, Bigham AS, Aali E. Comparison of lidocaine, tramadol, and lidocaine-tramadol for epidural analgesia in lambs. *Research in Veterinary Science*, 2011; 91(3): 434-438.
5. Vesal N, Ahmadi M, Foroud M, Imani H. Caudal epidural anti-nociception using lidocaine, bupivacaine or their combination in cows undergoing reproductive procedures. *Veterinary Anaesthesia and Analgesia*, 2013; 40(3): 328-332.
6. Baniadam A, Afshar FS, Ahmadian F. Analgesic effects of tramadol hydrochloride administered via caudal epidural injection in healthy adult cattle. *American Journal of Veterinary Research*, 2010; 71(7): 720-725.
7. Imani Rastabi H, Guraninejad S, Naddaf H, Hasani A. Comparison of the application of lidocaine, lidocaine-dexamethasone and lidocaine-epinephrine for caudal epidural anesthesia in cows. *Iranian Journal of Veterinary Research*, 2018; 19(3): 172-177.
8. Atiba A, Ghazy A, Gomaa N, Abouzeid T, Shukry M. Evaluation of Analgesic Effect of caudal epidural tramadol, tramadol-lidocaine, and lidocaine in water buffalo calves (*Bubalus bubalis*). *Veterinary Medicine International*, 2015; 2015: 1-6.
9. Weinberg L, Peake B, Tan C, Nikfarjam M. Pharmacokinetics and pharmacodynamics of lignocaine: A review. *World Journal of Anesthesiology*, 2015; 4: 17-29.
10. Tavakoli A. The epidural analgesic effects of Meloxicam in dogs. *Iranian Journal of Veterinary Science and Technology*, 2014; 6(1): 58-69.
11. Felipe GD, Henrique FV, Rego RO, Alves AP, Oliveira KD, Firmino MD, Medeiros LK, Silva GD, Batista LF, Dantas AF, Souza BB. Systemic and neurotoxic effects of epidural meloxicam in rabbits. *Ciência Rural*, 2017; 47(5).
12. Jasiecka A, Maslanka T, Jaroszewski JJ. Pharmacological characteristics of metamizole. *Polish Journal of Veterinary Sciences*, 2014; 17(1): 207-214.
13. Greene EM, Hagemann TM. Drug-Induced Hematologic Disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*, McGraw-Hill Education, New York, USA; 2017.
14. van den Bemt PM, Meyboom RH, Egberts AC. Drug-induced immune thrombocytopenia. *Drug Safety*, 2004; 27(15): 1243-1252.
15. Barash M, Reich KA, Rademaker D. Lidocaine-induced methemoglobinemia: a clinical reminder. *Journal of the American Osteopathic Association*, 2015; 115(2): 94-98.
16. Mulroy MF, Norris MC, Liu SS. Safety steps for epidural injection of local anesthetics: review of the literature and recommendations. *Anesthesia & Analgesia*, 1997 ;85(6): 1346-1356.
17. Grubb TL, Riebold TW, Crisman RO, Lamb LD. Comparison of lidocaine, xylazine, and lidocaine-xylazine for caudal epidural analgesia in cattle.

Veterinary Anaesthesia and Analgesia, 2002; 29(2): 64-68.

18. Bani Ismail Z. Epidural analgesia in cattle, buffalo, and camels. *Veterinary World*, 2016; 9: 1450-1455.
19. Araújo MA, Albuquerque VB, Deschk M, Santos GGF, Rodrigues CA, Oliva VNLS, Santos PSP. Cardiopulmonary and analgesic effects of caudal epidurally administered ropivacaine in cattle. *Veterinary Anaesthesia and Analgesia*, 2012; 39(4): 409-413.
20. Rioja E, Rubio-Martinez L, Monteith G, Kerr C. Analgesic and motor effects of a high-volume intercoccygeal epidural injection of 0.125% or 0.0625% bupivacaine in adult cows. *Canadian Journal of Veterinary Research*, 2013; 77: 273-280.
21. Acva T, Dvm D, Act R, Dvm MS. Comparison of lidocaine, xylazine, and lidocaine−xylazine for caudal epidural analgesia in cattle. *Veterinary Anaesthesia and Analgesia*, 2002; 29: 64-68.
22. Lee I, Yoshiuchi T, Yamagishi N, Oboshi K, Ayukawa Y, Sasaki N, Yamada H. Analgesic effect of caudal epidural ketamine in cattle. *Journal of Veterinary Science*, 2003; 4: 261-264.
23. Rostami M, Vesal N. The effects of adding epinephrine or xylazine to lidocaine solution for lumbosacral epidural analgesia in fat-tailed sheep. *Journal of the South African Veterinary Association*, 2012; 83: 1-7.
24. Kamiloglu A, Kamiloglu NN, Ozturk S, Atalan G, Kılıc E. Clinical assessment of epidural analgesia induced by xylazine-lidocaine combination accompanied by xylazine sedation in calves. *Irish Veterinary Journal*, 2005; 58(10): 567.
25. Plumb DC. *Plumb's Veterinary Drug Handbook*. 6th revised ed. Arnes, AI, Iowa State University Press, USA; 2008. 690-693, 1167-1168.
26. Kelly KR, Pypendop BH, Christe KL. Pharmacokinetics of tramadol following intravenous and oral administration in male rhesus macaques (Macaca mulatta). *Journal of Veterinary Pharmacology and Therapeutics*, 2015; 38(4): 375-382.
27. Lewis CA, Constable PD, Huhn JC, Morin DE. Sedation with xylazine and lumbosacral epidural administration of lidocaine and xylazine for umbilical surgery in calves. *Journal of the American Veterinary Medical Association*, 1999; 214(1): 89-95.
28. Mensink FJ, Kozody R, Kehler CH, Wade JG. Dose-response relationship of clonidine in tetracaine spinal anesthesia. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, 1987; 67(5): 717-721.
29. Marwaha J, Kehne JH, Commissaris RL, Lakoski J, Shaw W, Davis M. Spinal clonidine inhibits neural firing in locus coeruleus. *Brain Research*, 1983; 276(2): 379-383.
30. Popesko P G, R, Brown J. *Atlas of topographical anatomy of the domestic animals.*
31. Heuberger J, Schmidt S, Derendorf H. When is protein binding important? *Journal of Pharmaceutical Sciences*, 2013; 102(9): 3458-3467.
32. Torad FA, Hassan EA. Epidural lidocaine, nalbuphine, and lidocaine–nalbuphine combination in donkeys. *Journal of Equine Veterinary Science*, 2016; 37: 1-5.
33. Day T, Skarda R. The Pharmacology of local anesthetics. *The Veterinary clinics of North America Equine practice*, 1991; 7: 489-500.
34. Derossi R, Sampaio B, Varela J, Junqueira A. Perineal analgesia and haemodynamic effects of epidural administration of meperidine or hyperbaric bupivacaine in conscious horses. *The Canadian veterinary journal*, 2004; 45: 42-47.
35. Derossi R, Miguel G, Frazilio F, Nunes D, Kassab TA. L-bupivacaine 0.5% vs. racemic 0.5% bupivacaine for caudal epidural analgesia in horses. *Journal of Veterinary Pharmacology and Therapeutics*, 2005; 28: 293-297.
36. Derossi R, Verde-Selva A, Bertoni RA, Ruzzon R, Silva-Neto A. Lignocaine versus bupivacaine for flank anaesthesia using multiport catheters via a caudal epidural approach in cattle. *Australian Veterinary Journal*, 2010; 88: 362-367.
37. Mohammed NM, El-Drieny E, Eldurssi IS, El-Agory M. Effect of meloxicam on hematological and kidney histopathological changes in male mice. *Journal of Advances in Medicine and Medical Research*, 2017, 1-8.
38. Youssef M, Amin H, Abdalla M, Youssef A. Hematological and biochemical effects of meloxicam in male albino rats. *Current Science International*, 2017; 6(1): 23-23.
39. Ghazy A, Atiba A, Shukry M, Abouzeid T. Comparison of lidocaine and lidocaine-neostigmine for epidural analgesia in water buffalo calves (*Bubalus Bubalis*). *Alexandria Journal of Veterinary Sciences*, 2015; 46: 177.
40. Moulvi B, Parrah J, Kalim O, Athar H, Dedmari F. Haemato-biochemical response to lignocaine alone or in combination with xylazine for epidural analgesia

in cow calves. *Journal of Advanced Veterinary Research*, 2011.
41. Wagner A, Hinchcliff K. Cardiovascular effects of xylazine and detomidine in horses. *American Journal of Veterinary Research*, 1991; 52(5): 651-657.
42. Mwangi W, Mogoa E, Nguhiu J, Mulei C. The hematological and cardiopulmonary effects of epidural xylazine, lidocaine and their combination in acepromazine sedated dogs. *International Journal of Veterinary Sciences*, 2014; 3: 46-51.
43. Constable PD, Hinchcliff KW, Done SH, Grünberg W, Colwell DD, Connelly S, Dirikolu L, Gasser R, Hovda L, Ikede B, Larsen J, Witola W, Woolums AR. Veterinary Medicine, *11th ed.* 2017, 657-715.
44. Collinsworth KA, Kalman SM, Harrsion DC. The clinical pharmacology of lidocaine as an antiarrhythymic drug. *Circulation*, 1974; 50(6): 1217-1230.
45. de la Coussaye JE BJ, Eledjam JJ. Cardiac complications of local anesthetic agents. In: Vincent JL. eds, *Yearbook of Intensive Care and Emergency Medicine*, 1992, 129-136.