German Journal of Veterinary Research

eISSN:2703-1322

Research article

Evaluation of the anti-nociceptive effect of lidocaine-tramadol and lidocaine-medetomidine lumbosacral epidural anesthesia: A cross-over comparative study in goats

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Article History:
Received: 22-Nov-2023
Accepted: 26-Dec-2023
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Abstract

Small ruminants have a docile temperament and are typically operated under local or regional analgesia. In goats, lumbosacral anesthesia is the most commonly used regional anesthesia. This investigation aimed to evaluate the epidural anesthetic effects of lidocaine-medetomidine (LID-MED) and lidocaine-tramadol (LID-TRM) combinations in relation to cardiopulmonary effects. An experiment using a cross-over design was conducted on eight goats. The first group (LID-MED) was injected with lidocaine hydrochloride and medetomidine hydrochloride. The second group (LID-TRM) was injected with lidocaine hydrochloride and tramadol hydrochloride. The onset of analgesia, recumbency time, and standing time were recorded once, while scores were recorded periodically. Locomotor and anti-nociception scores were evaluated at baseline, 5, 10, 15, 30, 60, 90, and 120 minutes (min) post-anesthesia. Similarly, cardiorespiratory values were also recorded at the same intervals in each group. In the LID-MED receiving group, analgesia and recumbency onset were earlier, with a longer recumbency period. The LID-MED group showed a significant loss of sensation in all examined regions. The locomotor score revealed hind limb paralysis for 90 min in the LID-TRM group, while it continued for 120 min in the LID-MED group. In both LID-TRM and LID-MED groups, there was significant hypothermia; however, bradycardia was noticed in the LID-MED group from 5 min post-injection. Respiratory depression was also detected in the LID-MED group. The study revealed that lumbosacral epidural anesthesia using LID-TRM co-infusion produces reasonable and short duration (60 min) analgesia. In contrast, epidural lumbosacral injection of LID-MED co-infusion produces a longer duration of analgesia and recumbency.

Keywords: Epidural analgesia, Goats, Medetomidine, Tramadol

Citation: Al-Ali, F. T., Almubarak, A. I., Marzok, M., El-Deeb, W. M. and El-Hawari, S. F. 2023. Evaluation of the anti-nociceptive effect of lidocaine-tramadol and lidocaine-medetomidine lumbosacral epidural anesthesia: A cross-over comparative study in goats. Ger. J. Vet. Res. 3 (4): 20-24. https://doi.org/10.51585/gjvr.2023.4.0066

Introduction

Epidural anesthesia is commonly used in veterinary practice to perform diagnostic, obstetrical, and surgical interventions on domestic animals. The desensitized areas include the perineal region, inguinal region, and upper part of the hind limbs (Skarda and Tranquilli, 2007; Khajuria et al., 2014). Although previous literature described new locations for epidural injection (Awaad, 2018) (between the 5^{th} and 6^{th} lumbar vertebrae), lumbosacral space injection is more frequently used than other techniques (Lemke and Dawson, 2000; Marzok et al., 2022). In terms of epidural anesthetics, lidocaine is the most commonly used, although mepivacaine, bupivacaine, and procaine may also be used (Skarda and Tranquilli, 2007; Rioja Garcia, 2015).

The anesthesia provided by these agents, with the exception of bupivacaine, is of relatively short duration and may require re-administration before the procedure can be completed. Lidocaine is commonly used in small ruminants to conduct lumbosacral epidural anesthesia (Khajuria et al., 2014). Further, local anesthetics desensitize both sensory and motor nerves, which may result in undesired effects such as ataxia, hindlimb weakness, or motor paralysis (Lemke and Dawson, 2000; Skarda and Tranquilli, 2007; Garcia, 2021). An alternative analgesic combination utilizing different effective anesthetic combinations is required to prolong epidural anesthesia time because of its short duration of action (Marzok et al., 2022).

The combination of epidural injections with various types of medications has been described previously in small ruminants. Several studies have shown that opioids, epinephrine, and alpha-2 adrenergic agonists can be combined with lidocaine to provide long-lasting and adequate analgesia (Kinjavdekar et al., 2000; Bigham and Shafiei, 2008; Bigham Sadegh et al., 2009; Condino et al., 2010; Dehkordi et al., 2012). Furthermore, tramadol plus lidocaine produced a rapid and longer duration of anesthesia in goats than lidocaine alone (Dehkordi et al., 2012).

To our knowledge, there was a lack of literature comparing the anesthetic effect of epidural anesthetic agents in goats. The present study was designed to compare the anti-nociceptive and locomotor effects of lidocaine-medetomidine (LID-MED) and lidocaine-tramadol (LID-TRM) lumbosacral epidural injections in addition to recording the adjuvant cardiorespiratory parameters.

Table 1: Descriptive data of the numerical score used for anti-nociception evaluation in goats.

Anti-nociception score	Description
0 (no analgesia)	Animals refused stimulus and reacted strongly to movement.
1 (mild analgesia)	Animals showed skin shivering with mild reaction to both stimuli (pin prick and clamping).
2 (moderate analgesia)	Animals showed skin shivering against one stimulus only.
3 (complete analgesia)	Animals only reacted slightly to deep pinprick stimuli (penetrating the whole skin layer).
4 (deep analgesia)	Animals showed no reaction against deep pinprick and clamping stimuli.

Table 2: Anti-nociceptive scores in both lidocaine-tramadol (LID-TRM) and lidocaine-medetomidine (LID-MED) lumbosacral injections at different body regions.

Duration	LID-TRM						LID-MED					
	Tail	Perineal	Inguinal	Hindlimb	Flank	Umbilical	Tail	Perineal	Inguinal	Hindlimb	Flank	Umbilical
Baseline	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)
5 min	4 (4-4)*	4 (4-4)*	4 (4-4)*	4 (4-4)*	4 (4-4)*	4 (4-4)*	4 (4-4)*	4 (4-4)*	4 (4-4)*	4 (4-4)*	4 (3-4)*	4 (3-4)*
10 min	4 (4-4)*	4 (4-4)*	4 (4-4)*	4 (4-4)*	4 (4-4)*	4 (3-4)*	4 (4-4)*	4 (4-4)*	4 (3-4)*	4 (3-4)*	3 (3-4)*	3 (3-4)*
15 min	4 (3-4)*	4 (4-4)*	4 (4-4)$^{\dagger *}$	4 (4-4)*	4 (4-4)*†	4 (4-4)$^{\dagger *}$	3 (3-4)*	4 (3-4)*	3 (3-3)$^{\dagger *}$	4 (3-4)*	3 (2-3)†	3 (2-3)*
30 min	4 (3-4)*	4 (3-4)*	4 (4-4)*	4 (4-4)*	3 (3-4)*	3 (3-4)*	3 (2-4)*	3 (2-4)*	4 (3-4)*	3 (3-4)*	3 (2-4)*	3 (2-3)*
60 min	4 (4-4)$^{\dagger *}$	4 (4-4)*	4 (4-4)*	4 (3-4)*	3 (3-3)*	3 (3-3)*	3 (3-3)$^{\dagger *}$	4 (2-4)*	4 (2-4)*	3 (3-3)*	3 (2-3)	2 (2-3)
90 min	4 (3-4)$^{\dagger *}$	4 (4-4)$^{\dagger *}$	4 (4-4)$^{\dagger *}$	4 (4-4)*	4 (3-4)*	3 (3-4)*	2 (2-3)†	2 (2-3)†	3 (2-3)†	2 (2-4)	3 (2-3)	3 (2-3)
120 min	4 (3-4)$^{\dagger *}$	4 (3-4)$^{\dagger *}$	4 (4-4)$^{\dagger *}$	4 (4-4)$^{\dagger *}$	3 (3-4)$^{\dagger *}$	3 (3-4)$^{\dagger *}$	2 (1-2)†	2 (2-3)†	3 (2-3)†	2 (2-2)†	2 (1-2)†	2 (1-2)†

*Significant difference than baseline. †Significant difference between groups. *p-value* <0.05 is significant.

Materials and Methods

Animals and study design

The present study was conducted according to the Animal Care Committee of King Faisal University (Reference no. KFU-REC-2023-ETHICS1361). A total of eight clinically healthy, non-pregnant female mixed-breed goats were used in the experiment. Goats aged between 2.5 and 4 years old, and their body weight was 37.5±4.5 kg.

The study was conducted using a cross-over design with a washout interval of 10 days (El-Hawari et al., 2022). To allow the goats to acclimate, they were restrained in the operating room for two hours prior to lumbosacral injection. The injection site was clipped, cleaned, and disinfected; the injection was done while goats were in a standing position using a hypodermic, 18-gauge, 4.8 cm length needle. The success of needle placement was judged either through suction of the hanging drop from the needle hub or easy and no resistance injection. For the first group (LID-MED), lidocaine hydrochloride 2% (Lidocaine Hydrochloride injection®, Pharmaceutical Solution Industry, Jeddah, Saudi Arabia) was injected at a dose of 2.86 mg/kg (Dehkordi et al., 2012) followed with 20 μg/kg of medetomidine hydrochloride (Domitor®, Zoetis, New Jersey, USA) (Mpanduji et al., 2001). Both drugs were injected together in one syringe. In the second group (LID-TRM), lidocaine hydrochloride 2% was administered at a dose of 2.86 mg/kg and tramadol hydrochloride at a dose of 1 mg/kg (Dehkordi et al., 2012) (Tramal®, Grunenthal GmbH, Germany).

Experimental evaluation

The epidural injection time was considered zero time. The onset of analgesia is defined as the loss of sensation in the tail. Time of recumbency and time of unaided standing after recumbency were recorded. The period of recumbency was calculated by subtracting the time of recumbency from the time of unaided standing. Loss of sensation (anti-nociception score) was tested using a pinprick test (18-gauge needle) and pressure from a hemostatic clamp (closed to the first rachet). The stimulus was applied to the perineal, inguinal, hind limb, flank, and umbilical regions. In each region, animal responses were measured with numerical scores, where 0 indicates no analgesia, 1 indicates mild analgesia, 2 indicates moderate analgesia, 3 indicates complete analgesia, and 4 indicates deep analgesia (Table 1). Loss of sensation was assessed before epidural injection (baseline) and at 5, 10, 15, 30, 60, 90, and 120 min post-injection.

Locomotor scores, including the ability of the goats to walk and the degree of ataxia, were evaluated. To assess ataxia, a simple numeric scale was utilized: 0 indicates normal movement, 1 indicates mild ataxia (slight stumbling, but easily able to continue walking), 2 indicates moderate ataxia (marked stumbling, walking but extremely ataxic), 3 indicates severe ataxia (unable to walk and dragging the hindlimb), and 4 indicates an animal in a recumbent position. In each group, cardiovascular parameters, including heart rate, respiratory rate, and rectal temperature, were measured simultaneously with anti-nociception and locomotor score measurements.

Statistical analysis

The Shapiro-Wilk test was used to determine the normality of all obtained data. The anti-nociception and locomotor scores were nonparametric and expressed as medians (minimum to maximum), while the onset of analgesia, recumbency and unaided standing time, and recumbency period were parametric and expressed as means and standard deviations. Non-parametric data were analyzed using the Mann-Whitney U test, while parametric data were analyzed using a paired t-test. The significance of a value was determined when the *p-value* was ≤0.05.

Results

The success of epidural injection in this study was judged through suction of hanging drop from the hub of the needle in 5 goats, while it was judged via easy and no resistance injection in 3 goats. The onset of analgesia started later (73.50±17.69 sec) in the LID-TRM group than in the LID-MED group (38.67±19.16 sec) (*p-value* = 0.004). Goats in the LID-MED group showed significant early recumbency after epidural anesthesia (103.75±77.74 sec) than goats in the LID-TRM group (177.50±78.47 sec) (*p-value* = 0.034). Significant differences were detected in standing time and recumbency period between LID-TRM (76.25±17.97 min and 73.29±18.46 min, respectively) and LID-MED (182.50±19.33 min and 180.77±20.17min respectively) groups (*p-value*= 0.004 and 0.004 respectively).

According to the anti-nociception score in the LID-MED group, there was a significant loss of sensation compared to the baseline in all examined regions. It continues till 2 hours post epidural injection (Table 2). While in the LID-TRM group, normal sensation in flank and umbilical regions returned back by 60 min post epidural injection. However, all examined regions recovered sensation at 90 min post epidural injection. There was a significant loss of sensation in the tail area in the LID-MED group than LID-TRM at 60, 90, and 120 min post injection (*p-value*= 0.025, 0.01, and <0.001, respectively). By 90 min post epidural injection, perineal and inguinal regions desensitization elapsed later in the LID-MED group than in the LID-TRM group

Table 3: Locomotor scores in both lidocaine-tramadol (LID-TRM) and lidocaine-medetomidine (LID-MED) groups.

Duration	LID-TRM	LID-MED
Baseline	1 (1-1)	1 (1-1)
5 min	4 (3-4)*	4 (4-4)*
10 min	4 (4-4)*	4 (4-4)*
15 min	3.5 (3-4)*	4 (3-4)*
30 min	3.5 (3-4)*	4 (3-4)*
60 min	3.5 (3-4)*	4 (3-4)*
90 min	2.5 (2-3)†*	3.5 (3-4)†*
120 min	2 (1-3)†	3.5 (2-4)†*

*Significant difference than baseline. †Significant difference between groups. *p-value* <0.05 is significant.

Table 4: Cardiorespiratory changes accompanying lidocaine-tramadol (LID-TRM) and lidocaine-medetomidine (LID-MED) epidural injection in goats.

Duration	LID-TRM			LID-MED		
	HR	**RR**	**TEMP**	**HR**	**RR**	**TEMP**
Baseline	100.75±11.87	21.50±5.97	39.62±0.25	82.50±7.14	38.50±1.73	39.75±0.29
5 min	114.50±15.26	21.25±4.72	40.00±0.41	46.50±2.52*	30.25±0.5	40.00±0.41
10 min	104.00±13.37	21.50±5.69	40.00±0.37	42.00±1.63*	25.50±1.73*	40.00±0.41
15 min	97.00± 10.86	25.00±8.87	40.12±0.25	42.00±0.82*	22.75±2.06*	40.12±0.25
30 min	98.00±13.27	19.50±4.43	39.77±0.21	37.50±8.66*	21.00±6.63*	39.77±0.21
60 min	82.00±15.56	22.00±6.93	39.57±0.15	31.75±2.99*	25.00±8.16*	39.57±0.15
90 min	95.25±10.50	23.00±3.46	39.27±0.39	46.75 ±14.43*	17.00±5.03*	39.27±0.39
120 min	97.25±10.11	23.00±7.39	38.80±0.54*	59.00 ±2.71*	16.00±0.82*	38.80±0.54*

HR = Heart Rate; RR = Respiratory Rate; TEMP = rectal temperature. *Significant differences than baseline when *p-value* <0.05

(*p-value* <0.001 and 0.034, respectively). By 2 hours post epidural injection, all tested regions showed more desensitization in the LID-MED group than in the LID-TRM group.

Compared with the baseline, the results of the locomotor score revealed the presence of hind limb locomotor disturbance starting from the beginning of epidural injection and continued till 90 min in the LID-TRM group, while it continued till 120 min in the LID-MED group. Also, there was significant hind limb paralysis in the LID-MED group more than in the LID-TRM group at 90 and 120 min post-injection (*p-value* = 0.032 and 0.036, respectively) (Table 3).

Considering cardiorespiratory values, there was significant hypothermia in the LID-TRM and LID-MED groups than the baseline at 120 min post epidural injection (*p-value*= 0.046 and 0.016, respectively). Results also revealed significant bradycardia in the LID-MED group than the baseline started at 5 min post-injection and continued till 120 min. There was a decrease in respiratory rates at 10, 15, 30, 60, 90, and 120 min post epidural injection in the LID-MED group than the baseline (*p-value*= 0.005, <0.001, <0.001, 0.004, <0.001 and <0.001 respectively) (Table 4).

Discussion

Compared with pet animals, goats have limited epidural anesthesia literature. However, lumbosacral epidural injections are widely used by veterinarians for regional anesthesia in goats to resolve a variety of surgical and obstetrical challenges (Lemke and Dawson, 2000; Skarda and Tranquilli, 2007; Khajuria et al., 2014; Martin-Flores et al., 2023). The success of needle insertion in appropriate lumbosacral space was achieved by suctioning the hanging drop from the needle hub, followed by the flow of anesthetic drug without resistance (Khajuria et al., 2014). Only three out of eight goats showed no response to the hanging drop technique in the current study, which might be attributed to a narrow spinal canal and insufficient negative spinal pressure. Nevertheless, extradural pressure waves have not been reported as useful in confirming correct extradural needle placement in goats (Mpanduji et al., 2000; Iff et al., 2009).

Previous studies have reported that epidural injection of xylazine alone delays the onset of analgesia in goats (mean onset of analgesia, 9.0 min-9.5 min) (DeRossi et al., 2003) and bulls (mean onset of analgesia, 8.9±1.5 min) (Pagliosa et al., 2015). In contrast, Rostami and Vesal (2012) demonstrated the early onset of analgesia after lidocaine-xylazine epidural injection in sheep (3.4 min). However, early onset of analgesia (38.67±19.16 sec) and early recumbency (103.75±77.74 sec) were observed in the present study in the LID-MED group. This may be attributed to the sedative and analgesic effect of medetomidine (α2-adrenergic receptor agonists) (Rostami and Vesal, 2012; Pagliosa et al., 2015). Furthermore, previous studies conducted with epidural injections of xylazine-lidocaine combination and medetomidine alone demonstrated higher and more rapid onsets of analgesia (3.4 min and 2.75 min, respectively) (Lucky et al., 2007; Rostami and Vesal, 2012). Goats in the LID-MED group showed earlier recumbency than goats in the LID-TRM group as a result of the sedative effect of medetomidine (Mpanduji et al., 2000). Additionally, a significant difference was observed between the LID-MED and LID-TRM groups regarding the duration of recumbency and time of unaided standing following epidural anesthesia, which may be explained by the fact that α2-adrenoceptor agonists provide local drug depots (Akbar et al., 2014).

Epidural injections typically result in desensitized regions that are affected by the amount of drug injected and the animal's posture during the procedure (Lucky et al., 2007; Garcia-Pereira, 2018). In the present study, bilateral desensitization included the tail, perineal, inguinal, hind limb, flank, and umbilical regions. An epidural anesthetic injection has been reported to result in profound analgesia extending to the thorax, forelimbs, neck, and head (Mpanduji et al., 2000; Khajuria et al., 2014). Unfortunately, we did not record the anti-nociception score for the thorax, neck, and head. The anti-nociception score in the LID-TRM group showed that desensitization had disappeared by 90 min post-infusion in all examined regions. A similar result was obtained in sheep anesthetized with lidocaine only (60-120 min) (Rostami and Vesal, 2012) and less than that in goats anesthetized with LID-TRM epidurally (130±10 min) (Ragab et al., 2017). These differences may be due to the difference in animal position and gravity effect during epidural injection (lateral recumbency in the previous study versus standing position in the present study) (Lucky et al., 2007; Rostami and Vesal, 2012). However, the distribution of anesthetic agents to one animal side will continue for longer duration than if distributed to both sides.

The longer duration of desensitization of LID-MED than LID-TRM may probably be due to the fact that α2-adrenoceptor agonists provide a local depot of the drug (Grubb et al., 1992; Akbar et al., 2014). The first two regions recovered in the LID-TRM group were the flank and umbilical regions. Due to the distance between these regions and the injection site, a faster recovery has been observed than in the nearest regions (Kinjavdekar et al., 2000). By 120 min, there was significant desensitization in the LID-MED group more than LID-TRM in all examined regions and this may be due to medetomidine's superior anesthetic effect than tramadol. The same results have been observed in intravenous anesthetized dogs (El-Hawari et al., 2022).

In goats, hind limb ataxia is one of the undesirable side effects of lumbosacral epidural analgesia. A 90-minute duration of hind limb paralysis was observed in the LID-TRM group, whereas a 120-minute duration of ataxia was observed in the LID-MED group. A similar effect was described previously in goats injected with lidocaine-tramadol epidurally (Ragab et al., 2017) and in goats injected with medetomidine in the subarachnoid space (Kinjavdekar et al., 2000). At 90 and 120 min post epidural injection, there was a greater degree of ataxia in LID-MED than LID-TRM, which might be explained by the stronger sedative and muscle relaxant effects of α2-adrenoceptor agonists compared to tramadol (Oguntoye et al., 2022).

In both groups, hypothermia was observed 120 min post-injection, which may be due to generalized recumbency and a decrease in metabolic rate (Carroll et al., 2005; Akbar et al., 2014; Tanaka et al., 2014). Bradycardia and respiratory depression were observed only in the LID-MED group, starting 5-10 min after epidural injection and remaining throughout the observation period (Carroll et al., 2005; Akbar et al., 2014; Clarke and Trim, 2013). Previous studies conducted on ruminants using medetomidine reported similar findings (Singh et al., 2005). Additionally, as an α-2 agonist, medetomidine is also used for the treatment of hypertension (Mavropoulos et al., 2014).

In summary, lidocaine-tramadol and lidocaine-medetomidine epidural anesthesia provide satisfactory anesthesia for tail, perineal, inguinal, flank, and hind limb surgery in goats. However, lumbosacral epidural anesthesia using a lidocaine-tramadol combination produces reasonable and short duration (60 min) analgesia for tail, perineal, inguinal, and hind limbs in goats, but using this combination provides only 30 min of analgesia for flank and umbilical regions. The produced analgesia is usually accompanied by an undesirable ataxia ranging from moderate to severe. In contrast, epidural lumbosacral injection of lidocaine and medetomidine produces a longer duration of analgesia, suitable for 2 hours of surgery, with a longer duration of recumbency and a severe form of ataxia. Analgesia includes the tail, perineal, inguinal, hind limb, flank, and umbilical regions. To avoid tympany resulting from longer recumbency duration, animal fasting is necessary.

Bradycardia and respiratory depression must be monitored when the lidocaine-medetomidine combination is injected epidurally. An important limitation of this study is that surgical stimulus was not applied during the evaluation and that the antinociception and locomotor evaluations were not continued for more than two hours following injection. Additionally, hematological parameters should be examined during epidural administration to examine the pharmacokinetics of these combinations.

Article Information

Funding. The Deanship of Scientific Research, King Faisal University (GRANT 5,230).

Conflict of Interest. The authors declare no conflict of interest.

Authors contribution. Conceptualization: El-Hawari S, Almubarak A, Marzok M, El-Deeb W, Al-Ali F; Data curation: El-Hawari S, Almubarak A, El-Deeb W; Formal analysis: El-Hawari S, Marzok M, El-Deeb W, Al-Ali F; Investigation: El-Hawari S, Almubarak A; Methodology: El-Hawari S, Marzok M, El-Deeb W, Al-Ali F; Visualization: El-Hawari S; Writing original draft: Almubarak A, Marzok M, Al-Ali F; Reviewing final manuscript: El-Hawari S, El-Deeb W.

Acknowledgments. Authors acknowledge the Deanship of Scientific Research at King Faisal University for the financial support (GRANT 5230).

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