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Serum interleukin-6 and associated nociceptive parameters following subcutaneous infiltration of lidocaine alone, tramadol alone, and their combination in red Sokoto goat undergoing rumenotomy

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Abstract: The clinical practice of combining one or more drugs is gaining attention for enhancing efficacy, leading to quicker onset of action, longer duration of effect and minimising side effects. Previous studies showed that combining lignocaine and tramadol in an epidural injection significantly extended the duration of analgesia produced when compared to the use of lignocaine alone. The significance of this study is aiming toward improved pain management during surgery, especially in goats. In this study, the analgesic effects of subcutaneously administered lignocaine alone (7 mgkg-1), tramadol alone (3 mgkg-1), and their respective combination of 3.5 and 15 mgkg-1 on pain in goats undergoing rumenotomy were compared. The experiment was carried out on fifteen healthy (N=15) Red Sokoto goats. Blood was drawn from the jugular vein at seven distinct time intervals during the course of the experiment (0, 1, 2, 3, 4, 5, 6 and 7 hours) and serum was extracted. The severity of pain was ascertained by measuring serum level of IL-6 and the nociceptive response to a pain stimulus using a clinical algometer. This study revealed that the combination of lidocaine (03.78 minutes) and tramadol (3.68 minutes) has a quicker onset of action (2.01±0.42 minutes) and a more extended duration of activity (79.5 minutes) when compared to lidocaine (60 minutes) and tramadol (55.75 minutes) administered separately. There was no significant difference (P>0.05) in serum IL-6 before and after the administration of lidocaine, tramadol, or their combination. This study has demonstrated that the lidocaine-tramadol combination at respective doses of 3.5 and 1.5 mgkg-1 has a quicker onset and longer duration of activity when subcutaneously administered at the surgical site, in comparison with lidocaine alone and tramadol alone at respective doses of 7 and 3 mgkg-1. However, there was no remarkable difference in the serum pain biomarker (IL-6) among the three different treatments. Subcutaneous infiltration of the combination of lidocaine at 3.5 mgkg-1 with tramadol at 1.5 mgkg-1 via the inverted L block technique can be employed as an alternative to conventional lidocaine alone to achieve loco-regional analgesia for a more prolonged duration in goats to conduct laparotomy. Clinically, this drug combination could be useful in surgeries requiring extended regional anaesthesia, reducing the need for repeated dosing, hence improving animal welfare.

Keywords: *Interleukin-6, Loco-regional analgesia, Lidocaine, Nociceptive, Rumenotomy, Tramadol.*

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1. Introduction

Nociception is the physiological pathway that underpins the conscious feeling of pain [1] it is also considered as the neurological process of encoding noxious stimuli [2]. If there is no chemical intervention that will stop or hinder the transduction, transmission and modulation of nociceptive stimuli, the nociception may continue unimpeded during general anaesthesia [3].

Lidocaine is an acetamide local anaesthetic agent, its action is by altering the fast voltage-gated sodium channels at the neuronal cell membrane to impede signal transmission [4, 5]. It can be utilised for local, neuraxial, regional or peripheral anaesthesia, as well as the prevention or treatment of life-threatening ventricular arrhythmias, through infiltration, block, or topical application. It is also commonly used to treat chronic and neuropathic pain, as well as postoperative analgesia and surgical recovery as reported by Yakubu, et al. [6].

Tramadol is a synthetic derivative of codeine that functions by interacting with opioid receptors in the brain and spinal cord. It also inhibits the re-uptake of noradrenaline and serotonin, which controls monoaminergic spinal pain [7, 8]. The active metabolite, O-desmethyl tramadol, after biotransformation, is six times more powerful than tramadol and has a 200-fold higher affinity for neuronal receptors [7]. Tramadol and its metabolites impede noradrenaline reuptake and serotonin release by acting as μ receptor agonists, it has been reported that it could be used instead of morphine to offer perioperative analgesia for surgical procedures in many animal species [7].

In goats, sheep, and water buffalo, epidurally administered combinations of lidocaine and tramadol were examined. The combination, when compared to epidural lidocaine injection alone, produced a considerably longer duration of analgesia [3, 8-10]. The practice of combining two or more anaesthetic or analgesic agents to assist in the induction and maintenance of anaesthesia or analgesia, as the case may be, has garnered significant attention amongst researchers nowadays [11, 12]. In most cases, the purpose of this combination is to generate a more potent target response while minimising individual pharmacological side effects, leading production of synergistic long-duration activity [7]. In a previous study, epidural injection of lignocaine alone resulted in a faster onset of anaesthesia and longer duration of recumbency in goats, whereas epidural injection of tramadol resulted in the animals remaining upright but with poor analgesia quality [13]. An epidural combination of lignocaine and tramadol was found to have a significantly longer duration of analgesia than lignocaine injection alone based on a study conducted by Habibian, et al. [9]; Ayman, et al. [10].

Cytokines are low-molecular-weight soluble polypeptide molecules produced by a wide range of cells that do not appear to play a role in homeostasis in normal settings, but can be activated and released by a number of factors including infection, cancer, trauma, surgery, and inflammation [14]. There are a considerable number of inflammatory cytokines that have been reported to be released during nociceptive response to stimuli, the most notably reported being monocytes, macrophages, mastocytes, fibroblasts, B and T cells, endothelial cells, keratinocytes, smooth muscle cells, gastrointestinal parenchyma, and endometrial stroma cells, as well as neoplastic cells, which are the most common cytokine-producing cells [15].

Interleukin 6 (IL-6) is a key biomarker for pain and stress in mammals due to its central role in inflammation and immune responses. Following tissue injury or inflammation, IL-6 is rapidly synthesised and stimulates acute-phase proteins like C-reactive protein (CRP), which are indicators of systemic inflammation linked to pain. It also regulates blood iron and zinc levels by inducing hepcidin and ZIP14 expression, leading to hypoferraemia and hypozincaemia commonly observed in inflammatory responses as reported by Nemeth, et al. [16]; Liuzzi, et al. [17]. Furthermore, IL-6 affects immune cell differentiation, promoting Th17 cells while inhibiting Treg cells, which can exacerbate chronic inflammatory conditions associated with pain [18-20]. IL-6 also enhances platelet production, vascular permeability, and angiogenesis, commonly seen in painful inflammatory lesions [21, 22]. In animals, IL-6 is a useful objective measure of discomfort [23, 24] it was reported by Biobaku, et al. [25] that IL-6 can be used as a biomarker of stress in goats. It appears there is no literature that reported the use of IL-6 as a specific biomarker of pain assessment in goats other that it used for the detection general stress. The cytokine's role in the regulation of pain has been the subject of numerous research studies. Increased pain and hyperalgesia are associated with a variety of pathological

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conditions, and the pleiotropic cytokine IL-6 is significantly upregulated [7]. The levels of Serum IL-6 are raised in patients with neurological problems, musculoskeletal traumas, and autoimmune and inflammatory illnesses [24].

This study aimed to evaluate and compare the analgesic quality of subcutaneous infiltration at the surgical site between lidocaine, tramadol and their combination in goats undergoing rumenotomy. We hypothesised that subcutaneous administration of lidocaine and tramadol may enhance the loco-regional analgesia in goats undergoing rumenotomy.

2. Materials and Methods

2.1. Experimental Animals and Ethical Approval

This study was carried out in compliance with the ARRIVE guidelines. Ethical approval was sought from the Faculty Animal Research Ethics Committee of the Faculty of Veterinary Medicine, Usmanu Danfodiyo University, Sokoto, with the reference number UDUS/FAREC/2020/ AUP-R0-7. Animal welfare was a primary consideration, efforts have been made to minimize distress through pre- and post-operative monitoring, administration of analgesics when needed, and controlled environments that supported recovery. Welfare checks were implemented for all animals, including routine assessments for signs of pain, distress, or infection, and careful observation of animals post-operatively to ensure humane treatment. These protocols were aimed at upholding the highest standards of ethical conduct and animal care as recommended by ARRIVE.

Fifteen (N=15) apparently healthy goats (8 males and 7 females), with weights ranging between 18-25 kg and aged 9-16 months, were selected for this investigation. The sample size was determined through a power analysis set at 75% with an effect size of 75%, resulting in 15 animals. These animals were then divided into three groups, with five goats per group. They were observed and acclimatised under the same housing and feed regimen for two weeks, during which they were de-wormed using levamisole suspension (Troy Animal Care New Zealand) orally prior to the commencement of the experiment. Animals were fasted for 12 hours and water was withheld for 6 hours prior to surgery to decrease the chances of regurgitation as described by Abubakar, et al. [26]. The left flank area was aseptically prepared with 4% Chlorhexidine gluconate (Savlon®, Vervaadingdeur, Johnson and Johnson (pty) Ltd, London).

2.2. Animal Grouping and Anaesthetic Protocols

The randomization process involved using a random number generator to assign the 15 healthy goats into three groups (A, B, and C), with five goats (n=5) allocated to each treatment group. Group A received lidocaine alone, Group B received tramadol alone, and Group C received a combination of lidocaine and tramadol. The use of a random number generator helped ensure that the assignment of animals was unbiased, aiming to create comparable groups. In group A, lidocaine Hcl 2% (Debocaine® ALDebeiky Pharmaceutical Industries Co.) was subcutaneously injected at 7 mg/kg using an inverted L block technique as described by Dehkordi and Bigham-Sadegh [8]. In group B, 5% tramadol hydrochloride (Koralodol®, AMRIY Pharmaceuticals) was subcutaneously injected using the same technique as in group A at a dose of 3 mg/kg body weight based on the previously reported dosage by Ajadi, et al. [13]. In group C**,** a mixture of tramadol hydrochloride and lidocaine at respective doses of 1.5 mg/kg and 3.5 mg/kg was subcutaneously injected using the same inverted L block technique at the flank region of the goats.

2.2. Anaesthetic Indices

The time interval (in minutes) from the subcutaneous injection of the drug to the loss of mechanical response to the clinical algometer in the flank region was defined as the onset of analgesia. The time interval (in minutes) from the loss and reappearance of pain response to the clinical algometer in the flank region was defined as the duration of analgesia as described by Buhari, et al. [27].

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2.4. Blood Sampling

Blood samples were collected from the jugular vein using 5 mL syringes for haematological parameters analysis at baseline (0 minute), and subsequently at 6 different timing intervals (1, 2, 3, 4, 5 and 6 hours) after drug administration based on the previous study conducted by Ayman, et al. [10].

2.5. Pain Assessment

The levels of serum interleukin-6 (IL-6), and mechanical pressure thresholds were measured at baseline and after surgery at certain timing intervals (1, 2, 3, 4, 5, 6 hours). Pain assessments were conducted by two independent observers that were blinded to the treatment allocations to eliminate any potential bias. The mechanical nociceptive thresholds were then measured using a clinical algometer (FPX25, Wagner instrument, Greenwich CT, USA), which records sensitivity to pressure according to the standard procedure described by Buhari, et al. [7] and Kaka, et al. [1]. Briefly, using the clinical algometer, a constant pressure was applied 2 cm away from the incision site, in the cranial, caudal, left lateral and right lateral directions. The pressure threshold was recorded at the point of a positive reaction, with an average of four readings taken per site. A positive reaction was deemed to be a leg shake, turning of the head towards the stimulus site, or vocalisation. The instrument was calibrated with a progressively increasing force, and a cut-off point of 15N was used to prevent mechanical damage to the skin. Increasing values with heightened pressure signified less discomfort, whilst decreasing values with minimal pressure denoted pain in that region.

2.6. Measurement of Serum IL-6

Serum IL-6 concentrations were determined before premedication and then 6 times after drug administration at 1-hour intervals. Blood samples (2 mL) were obtained from a jugular vein and centrifuged at 1000 revolutions per minute for 10 minutes. The serum was separated and kept for analysis with commercially available enzyme-linked immunosorbent assay (ELISA) kits (Abbkine Scientific Co., Ltd, Wuhan, China) specific for goats' IL-6. A wavelength of 450 nm was selected for optical density measurements on an ELISA micro plate reader (Bio-Rad model 680, Bio-Rad Laboratories Inc., Tokyo, Japan). The ELISA assay was performed in accordance with the ELISA kit guidelines.

2.7. Statistical Analysis

Values derived from mechanical pain threshold and serum levels of IL-6 were analysed using parametric statistical methods, ANOVA with repeated measure. The data were expressed as mean SD or SEM prior to comparison. Fisher's least significant difference (LSD) multiple comparison test was used to compare differences at each time point. A value of $P<0.05$ was considered to be significant.

3. Results

3.1. Onset and Duration of Analgesia

The onset of analgesia in the lidocaine treated group was 3.78 minutes (95% CI: 3.42–4.14) after administration, and the duration of analgesia was 60 minutes (95% CI: 54.5–65.5). The onset of analgesia for the tramadol treated group was 3.68 minutes (95% CI: 3.32–4.04) after administration, and the duration of action was 55.75 minutes (95% CI: 49.05–62.45). The onset of action for the lidocaine-tramadol treated group was shorter, indicating a rapid action (2.01 minutes, (95% CI: 1.59–2.43) after administration, and the duration of action was 79.5 minutes (95% CI: 72.9–86.1) (Table 1). There were significant differences among the treatment groups ($P< 0.05$).

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Table 1.
Anesthetic indices of subcutaneously administered lidocaine, tramadol and lidocaine-tramadol combination in goats undergoing rumenotomy, data were expressed as mean ± SD.

Anaesthetic indices	Lidocaine group; 7mg/kg (n=5)	Tramadol group; 3mg/kg (n=5)	Lidocaine-tramadol; 3.5, 1.5 mg/kg group (n=5)
Onset of analgesia (Minutes)	3.78±0.61	3.68±0.64	2.01±0.42*
Duration of analgesia (Minutes)	60±5.5	55.75±6.7	79.5±6.6*

Note: *Denote significant difference among the groups. The onset of action and duration of analgesia were measured in minutes.

3.2. Effects of Lidocaine, Tramadol, and Lidocaine-Tramadol on Interleukin 6 (IL-6)

After administration drugs under investigation, serum IL-6 levels fluctuated slightly during the sampling intervals. Initially, within the first 3 hours, the IL-6 levels appeared lower than at other time points across all treatment groups. Notably, the tramadol-alone group maintained a slightly lower serum IL-6 level than the other groups throughout the observation period. Although these fluctuations were present, statistical analysis showed no significant differences in IL-6 levels between groups or across time points within each group ($P > 0.05$; ANOVA with repeated measures) (Figure 1).

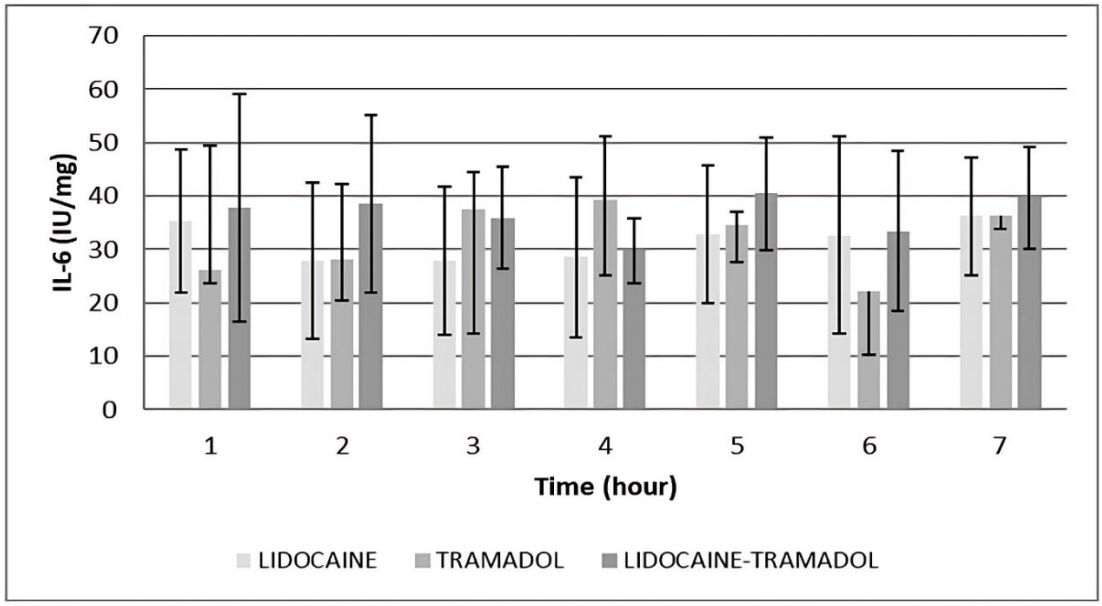

Figure 1.
Mean Interleukin-6 Levels over time. IL-6 levels are not significantly different within or between treatment groups throughout the study period.

3.3. Effects of Lidocaine, Tramadol, and Lidocaine-Tramadol on Mechanical Pain Threshold

Pain perception, measured as mechanical pain threshold, showed significant differences over time within each group and between groups ($P < 0.05$), although not all time points differed significantly between groups ($P > 0.05$) (Figure 2).

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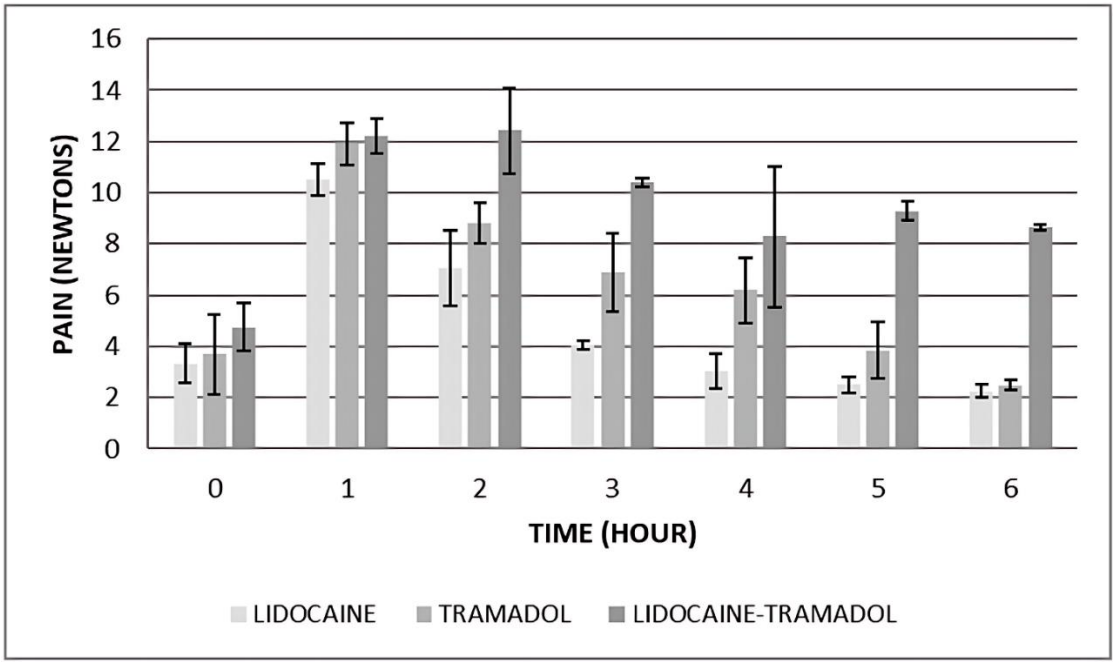

Figure 2.
Mean mechanical pain threshold in the three treatment groups at different sampling intervals.

4. Discussion

This study has demonstrated that subcutaneous administration of tramadol and lidocaine-tramadol combination in goats undergoing rumenotomy is an effective method for providing loc-regional pain control and with little or no systemic side effects on the goats. In this study, the onset of action was shorter in the lidocaine-tramadol treated group than in the lidocaine and tramadol alone groups.

The duration of action in the lidocaine alone treated group exceeded that of the tramadol alone treated group. However, the duration of action in the lidocaine-tramadol combination treated group was longer than the lidocaine alone and tramadol alone groups. There have been numerous studies on the synergistic effects between lidocaine and other agents. A study by Tabbi and Interlandi [28] found that combining tramadol with lidocaine provided effective intraoperative and postoperative pain management for the repair of umbilical hernia in pigs. Another study explored the effects of tramadol-lidocaine and butorphanol-lidocaine combinations on the minimum alveolar concentration (MAC) of sevoflurane in dogs, highlighting the synergistic effects of these drug combinations in reducing anaesthetic requirements and improving analgesia [29] the study reported a significant difference in terms of analgesic potency and duration of action between the group of animals that were administered with the combination of cocktails of drugs and the tramadol alone and lidocaine alone treated groups. This finding was similar to that observed previously in goat, lamb and water buffalo [9, 10] but contrary to the findings in West African Dwarf sheep [11]. The variation in analgesic potency of tramadol combinations observed in the West African Dwarf goat may be attributed to differences in relative stimulation of diverse pain receptors. It could also be related to genetic differences in these species of animals, in the sensitivity of the pain receptors as reported by Trescot, et al. [30].

There was a significant increase in the pain thresholds 1 hour following drug administration in all groups. There was no significant difference between the baseline threshold values in all groups. The pain threshold values significantly increased compared to baseline values for up to 6 hours in the lidocaine-tramadol group, for up to 4 hours in the tramadol group, and for up to 2 hours in the lidocaine group. This is similar to the findings of KuKanich, et al. [31] and Kaka, et al. [1].

The prolonged duration of pain relief in the lidocaine-tramadol treated group could be attributed to the synergistic effects of combining lidocaine with an opioid. Lidocaine offers prompt yet short-term

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pain relief by blocking sodium channels, whereas tramadol functions as an opioid and serotonin-norepinephrine reuptake inhibitor, thereby providing more prolonged and sustained central analgesia. This combination had enhanced and prolonged pain relief compared to using each drug alone, as supported by similar findings in studies by KuKanich, et al. [31]; Kaka, et al. [1] and Yoon and Choi [32].

Decreasing algometer values for the nociceptive thresholds commencing 3 hours post lidocaine administration, 5-6 hours after tramadol injection and 4 hours following lidocaine-tramadol administration, indicates an increased pain around the incision site. These findings suggest that the elevated pressure thresholds 1-hour post tramadol and lidocaine-tramadol administration is linked to adequate analgesia, a result similar to that of Buhari, et al. [7].

The serum IL-6 levels diminished gradually between the 2nd to 5th hours and 4th to 6th hours in the lidocaine and lidocaine-tramadol treated groups respectively. However, a significant increase in serum IL-6 was observed as compared to the baseline values after tramadol administration at 3rd to 6th hours; which is similar to the findings of Singh, et al. [33]; Costa, et al. [34] in oral and swine surgeries. Increase in IL-6 plasma concentrations have also been noticed in response to cardiopulmonary bypass Dreyer, et al. [35]. Pro-inflammatory and pro-nociceptive roles for IL-6 have been described in rats receiving intraplantar and intrathecal injections of IL-6 to induce hyperalgesia or allodynia [36].

IL-6 is often associated with inflammation and can be elevated in response to tissue injury or immune activation. The lack of significant differences in IL-6 between groups suggests that none of the treatments (lidocaine, tramadol, or their combination) induced notable systemic inflammation or immune activation following administration. The trend towards lower IL-6 in the tramadol group might suggest a mild anti-inflammatory effect; however, without significance, this remains speculative.

Mechanical pain threshold assessments indicate each drug's effectiveness in pain control over time. The significant differences observed suggest varying durations of analgesic efficacy across the treatments. The lidocaine-tramadol combination appears to extend analgesia duration and increase pain threshold values beyond those achieved by either drug alone, potentially reflecting the synergistic interaction between lidocaine's local anesthetic action and tramadol's central analgesic effects.

5. Conclusion

This study highlights that the lidocaine-tramadol combination (3.5 and 1.5 mg/kg, respectively) provides a quicker onset and longer duration of analgesic effect compared to lidocaine or tramadol alone in goats undergoing laparotomy. While the combination demonstrated effectiveness in prolonging analgesia, there was no significant difference in serum IL-6 levels among treatments, suggesting minimal impact on systemic inflammatory responses. Acknowledging the limitations of a small sample size and the lack of significant findings for IL-6, further research is essential to validate these results. Future studies should involve larger sample sizes, additional biomarkers, and consideration of different species to optimize analgesic protocols. Overall, this study suggests that the lidocaine-tramadol combination could serve as a promising alternative for achieving prolonged loco-regional analgesia in veterinary surgical settings, pending further investigation to enhance its application across diverse species and surgical contexts.

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References

[1] U. Kaka, H. C. Chen, Y. M. Goh, A. A. Abubakar, S. Fakurazi, and M. Ebrahimi, "Validation of a modified algometer to measure mechanical nociceptive thresholds in awake dogs," *BioMed Research International*, vol. 2015, no. 1, p. 375421, 2015. https://doi.org/10.1155/2015/375421

[2] U. Kaka *et al.*, "Pre-emptive multimodal analgesia with tramadol and ketamine–lidocaine infusion for suppression of central sensitization in a dog model of ovariohysterectomy," *Journal of Pain Research*, pp. 743-752, 2018. https://doi.org/10.2147/JPR.S152475

[3] S. Shamsudeen, S. B. Idris, A. A. Abubakar, and M. M. Abubakar, "Potentiating the epidural analgesic effect of lidocaine in uda sheep with xylazine and medetomidine," *Journal of Applied Veterinary Sciences*, vol. 9, no. 2, pp. 125-133, 2024. https://doi.org/10.21608/JAVS.2024.275091.1323

[4] W. Tranquilli and R. Skarda, *Local and regional anesthetic and analgesic techniques: Ruminant and swine, In: Lumb & Jones' Veterinary Anesthesia and Analgesia*, 4th ed. (IA: Blackwell Publishing). 2007.

[5] W. Knauer, E. Barrell, A. Guedes, and B. Ventura, "Effects of multimodal pain management strategies on acute physiological and behavioral response to cautery disbudding in neonatal goat kids," *Journal of Dairy Science*, vol. 106, no. 4, pp. 2830-2845, 2023.

[6] A. S. Yakubu *et al.*, "Evaluation of lumbo-sacral epidural anaesthesia or analgesia with lidocaine-acepromazine combination in dogs undergoing cystotomy," *International Journal*, vol. 6, no. 6, p. 204, 2020. https://doi.org/10.18203/issn.2454-2156.IntJSciRep20202095

[7] S. Buhari, K. Hashim, G. Yong Meng, N. M. Mustapha, and S. H. Gan, "Subcutaneous administration of tramadol after elective surgery is as effective as intravenous administration in relieving acute pain and inflammation in dogs," *The Scientific World Journal*, vol. 2012, no. 1, p. 564939, 2012. https://doi.org/10.1100/2012/564939

[8] A. Dehkordi and G. R. Bigham-Sadegh, "Evaluation of anti-nociceptive effect of epidural tramadol, tramadol-lidocaine and lidocaine in goats," vol. 39, no. 1, pp. 106-110, 2012. https://doi.org/10.1111/j.1467-2995.2011.00655.x

[9] S. Habibian, A. Bigham, and E. Aali, "Comparison of lidocaine, tramadol, and lidocaine–tramadol for epidural analgesia in lambs," *Research in Veterinary Science*, vol. 91, no. 3, pp. 434-438, 2011. https://doi.org/0.1016/j.rvsc.2010.09.023

[10] A. Ayman, A. Ghazy, N. Gomaa, T. Kamal, and M. Shukry, "Evaluation of analgesic effect of caudal epidural tramadol, tramadol-lidocaine, and lidocaine in water buffalo calves (Bubalus bubalis)," *Veterinary Medicine International*, vol. 2015, no. 1, p. 575101, 2015. https://doi.org/10.1155/2015/575101

[11] R. A. Ajadi, O. A. Sobanke, A. A. Adeniyi, A. A. Adeusi, A. Adebiyi, and A. K. Akinloye, "Influence of tramadol on anaesthetic indices and physiological parameters of epidural lignocaine in West African dwarf sheep undergoing laparo-ovariectomy," *Nigerian Journal of Physiological Sciences*, vol. 32, pp. 165-170, 2017.

[12] A. A. Abubakar, D. Gabriel, Y. A. Sadiq, L. F. Mobolaji, and M. M. Onoruoyiza, "Lumbosacral epidural analgesia with ketamine alone or in combination with xylazine in dogs," *International Journal of Veterinary Science*, vol. 4, no. 4, pp. 111-117, 2015.

[13] R. A. Ajadi, A. O. Owanikin, M. M. Martins, and O. S. Gazal, "Effect of epidural tramadol and lignocaine on physiological and behavioural changes in goats subjected to castration with a high-tension band," *New Zealand Veterinary Journal*, vol. 60, no. 6, pp. 344-348, 2012. https://doi.org/10.1080/00480169.2012.696576

[14] R. Ter Horst *et al.*, "Host and environmental factors influencing individual human cytokine responses," *Cell*, vol. 167, no. 4, pp. 1111-1124, 2016. https://doi.org/10.1016/j.cell.2016.10.018

[15] C. Liu, D. Chu, K. Kalantar-Zadeh, J. George, H. A. Young, and G. Liu, "Cytokines: From clinical significance to quantification," *Advanced Science*, vol. 8, no. 15, p. 2004433, 2021. https://doi.org/10.1002/advs.202004433

[16] E. Nemeth *et al.*, "IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin," *The Journal of Clinical Investigation*, vol. 113, no. 9, pp. 1271-1276, 2004. https://doi.org/10.1172/jci20945

[17] J. P. Liuzzi *et al.*, "Interleukin-6 regulates the zinc transporter Zip14 in liver and contributes to the hypozincemia of the acute-phase response," *Proceedings of the National Academy of Sciences*, vol. 102, no. 19, pp. 6843-6848, 2005.

[18] T. Korn, E. Bettelli, M. Oukka, and V. K. Kuchroo, "IL-17 and Th17 Cells," *Annual review of Immunology*, vol. 27, no. 1, pp. 485-517, 2009.

[19] E. Bettelli *et al.*, "Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells," *Nature*, vol. 441, no. 7090, pp. 235-238, 2006.

[20] A. Kimura and T. Kishimoto, "IL-6: Regulator of Treg/Th17 balance," *European Journal of Immunology*, vol. 40, no. 7, pp. 1830–1835, 2010.

[21] H. Nakahara *et al.*, "Anti–interleukin-6 receptor antibody therapy reduces vascular endothelial growth factor production in rheumatoid arthritis," *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, vol. 48, no. 6, pp. 1521-1529, 2003.

[22] M. Hashizume, H. Yoshida, N. Koike, M. Suzuki, and M. Mihara, "Overproduced interleukin 6 decreases blood lipid levels via upregulation of very-low-density lipoprotein receptor," *Annals of the Rheumatic Diseases*, vol. 69, no. 4, pp. 741-746, 2010.

[23] N. A. Rasmussen and L. A. Farr, "Beta-endorphin response to an acute pain stimulus," *Journal of Neuroscience Methods*, vol. 177, no. 2, pp. 285-288, 2009. https://doi.org/10.1016/j.jneumeth.2008.10.013

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Vol. 9, No. 1: 536-545, 2025
DOI: 10.55214/25768484.v9i1.4180

[24] C. Sommer and M. Kress, "Recent findings on how proinflammatory cytokines cause pain: Peripheral mechanisms in inflammatory and neuropathic hyperalgesia," *Neuroscience Letters*, vol. 361, no. 1-3, pp. 184-187, 2004. https://doi.org/10.1016/j.neulet.2003.12.007

[25] K. Biobaku, T. Omobowale, A. O. Akeem, A. Aremu, N. Okwelum, and A. Adah, "Use of goat interleukin-6, cortisol, and some biomarkers to evaluate clinical suitability of two routes of ascorbic acid administration in transportation stress," *Veterinary World*, vol. 11, no. 5, p. 674, 2018. https://doi.org/10.14202/vetworld.2018.674-680

[26] A. Abubakar, R. Andeshi, A. Yakubu, F. Lawal, and U. Adamu, "Comparative evaluation of midventral and flank laparotomy approaches in Goat," *Journal of Veterinary Medicine*, vol. 2014, no. 1, p. 920191, 2014. https://doi.org/10.1155/2014/920191

[27] S. Buhari *et al.*, "Postoperative analgesic efficacy of tramadol and diclofenac sodium in goats," *Sahel Journal of Veterinary Sciences*, vol. 17, no. 3, pp. 22-27, 2020.

[28] M. Tabbi and C. Interlandi, "Tramadol vs. Lidocaine administered intraperitoneally and in incisional lines for the intraoperative and postoperative pain management of romifidine telazol-anesthetized swine undergoing Umbilical Hernia Repair," *Animals*, vol. 13, no. 18, p. 2905, 2023. https://doi.org/10.3390/ani13182905

[29] S. Mastrocinque and D. Fantoni, "A comparison of the isoflurane sparing effects of lidocaine, fentanyl, and a lidocaine-fentanyl combination in dogs," *Veterinary Anaesthesia and Analgesia*, vol. 30, no. 4, pp. 190-199, 2003. https://doi.org/10.1111/vaa.12079

[30] A. M. Trescot, S. Datta, M. Lee, and H. Hansen, "Opioid pharmacology," *Pain Physician*, vol. 11, no. 2S, p. S133, 2008.

[31] B. KuKanich, B. D. X. Lascelles, and M. G. Papich, "Assessment of a von Frey device for evaluation of the antinociceptive effects of morphine and its application in pharmacodynamic modeling of morphine in dogs," *American Journal of Veterinary Research*, vol. 66, no. 9, pp. 1616-1622, 2005. https://doi.org/10.2460/ajvr.2005.66.1616

[32] M. H. Yoon and J. I. Choi, "Pharmacological synergism between intrathecal neostigmine and tramadol in rats," *Anesthesia & Analgesia*, vol. 113, no. 1, pp. 164-170, 2011. https://doi.org/10.1097/00000539-200002000-00033

[33] P. Singh *et al.*, "A prospective study to assess the levels of interleukin-6 following administration of diclofenac, ketorolac and tramadol after surgical removal of lower third molars," *Journal of Maxillofacial and Oral Surgery*, vol. 14, pp. 219-225, 2015. https://doi.org/10.1007/s12663-013-0609-1

[34] G. L. Costa *et al.*, "Tramadol vs. Lidocaine administered intraperitoneally and in incisional lines for the intraoperative and postoperative pain management of romifidine-telazol-anesthetized swine undergoing umbilical Hernia Repair," *Animals*, vol. 13, no. 18, p. 2905, 2023. https://doi.org/10.3390/ani13182905

[35] W. J. Dreyer *et al.*, "Interleukin 6 induction in the canine myocardium after cardiopulmonary bypass," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 120, no. 2, pp. 256-263, 2000. https://doi.org/10.1067/mtc.2000.108168

[36] R. F. De Jongh, K. C. Vissers, T. F. Meert, L. H. Booij, C. S. De Deyne, and R. J. Heylen, "The role of interleukin-6 in nociception and pain," *Anesthesia & Analgesia*, vol. 96, no. 4, pp. 1096-1103, 2003. https://doi.org/10.1213/01.ANE.0000055362.56604.78