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Original Research

Comparative effects of preemptive Tramadol and Pentazocine administration in dogs undergoing ventral midline laparotomy surgical procedures

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ABSTRACT

Ventral midline laparotomy surgery in dogs is regarded as a painful surgery with higher pain score and lower nociceptive threshold. This study evaluated the comparative effects of preoperative tramadol or pentazocine administration in dogs undergoing ventral midline laparotomy surgical procedures. Ten bitches were randomly allocated into two groups containing 5 dogs each. The bitches in each group were made to undergo either gastrotomy or ovriohysterectomy surgery. Group 1 received intarmuscular injection of 2mg/kg Pentazocine while group 2 received 2mg/kg Tramadol HCl intramuscularly 15 minutes before premedication with Xylazine (1mg/kg IM) and atropine (0.04mg/kg IM) while anaesthetic induction was achieved with intravenous administration of Ketamine (10mg/kg) and Diazepam (0.25mg/kg). Cardiopulmonary and anaesthetic parameters were monitored for 90 minutes while antinociception was also assessed by pedal withdrawal reflex. Data between the two groups were compared using independent sample T-test and values of $P \leq 0.05$ were considered significant. The quality of anaesthesia was better in the tramadol group with longer duration of antinociception (48.00±5.08minutes) compared to the pentazocine group (40.20±5.17minutes) which is not statistically significant ($p>0.05$). The TSD was significantly longer in the tramadol group (33.80±10.71min) compared to the pentazocine group (7.00±4.36min). The anaesthetic parameters did not differ significantly ($p>0.05$) between the pentazocine and tramadol group. There was no significant effect of anaesthesia on the cardiopulmonary parameters measured in both groups. Even though tramadol provide longer duration of antinociception, pentazocine is an alternative replacement in dogs undergoing laparotomy especially in developing countries where there is limited access to tramadol.

Keywords: Bitch, dogs, gastrotomy, laparotomy, ovariohysterectomy, Pentazocine, Tramadol

INTRODUCTION

Ventral midline laparotomy surgery is a painful surgery with higher pain score and lower nociceptive threshold when compared with pinhole laparoscopic surgery in dogs (Vasiljević *et al.*, 2015; Coutinho *et al.*, 2018). This thus underscore the importance of preemptive analgesia when carrying out such procedure in dogs. The use of analgesics to control surgical pain and its complications as well as improve animal welfare is an essential perioperative pain management protocol in dogs (Nazifi *et al.*, 2019; Hernández-Avalos *et al.*, 2021). A drug induced state of unconsciousness, amnesia, immobility, and antinociception is regarded as a state of general anaesthesia (Brown *et al.*, 2018; Cividjian *et al.*, 2017). There is continuous nociceptive signaling during general anaesthesia with a negative physiologic consequence as well as higher arousal risk (Shanthanna *et al.*, 2021). Reports have shown that there is a strong connection between nociceptive and arousal pathways such that administration of anti-nociceptive agents decreases arousal (Egan &Svensen, 2018). Nociception and initiation of central nervous system sensitization during surgery are usually prevented by inclusion of preemptive analgesia in the anaesthetic protocol and administered during perioperative phase before induction of noxious stimulus (Kissin, 2000). This therefore alleviates the response to future nociception resulting in painless stimulus throughout surgery, enhances anaesthetic quality as well as lower postoperative pain (Dilip *et al.*, 2019; Haffner *et al.*, 2019).

Multimodal analgesics is very key to surgical pain management and quality of anaesthesia (McEvoy *et al.*, 2017; Dunkman & Manning, 2018; Kaye *et al.*, 2019). Analgesia during surgery requires multimodal approach

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using combination of different analgesic drugs of varying mechanism of action (Domínguez-Oliva *et al.,* 2021; Hyland *et al.,* 2021). Ketamine as an adjunt to opoid in pain management has been reported to improve analgesia (Hyland *et al.,* 2021, Edwards *et al.,* 2019). Xylazine, an alpha-2 aderenagic agonist provides central analgesia without significant depression of respiratory apparatus making it essential for quality anaesthesia and analgesia (Hyland *et al.,* 2021).

Opioids are essential component of perioperative care where they provide antinociception and decrease arousal thereby improving animal recovery and alleviate post-surgical pain (Brown *et al.,* 2018; Egan, 2019; Alexander *et al.,* 2019). Tramadol is an atypical opioid that modifies the descending noradrenergic and serotonergic pathways while having a weak effect on μ-receptors (Vadivelu *et al.,* 2017). Conversely, pentazocine is an opioid partial agonist-antagonist that produces a potent analgesic effect through acting as a strong or weak antagonist at the μ receptor and as an agonist or partial agonist at the k receptor (Sadafule & Karhade, 2018).

Tramadol has been reported as an effective preemptive analgesic (Xuan *et al.,* 2022). However, co-administration of tramadol with other analgesics offers a better analgesia than tramadol monotherapy (KuKanich, 2019; Domínguez-Oliva *et al.,* 2021). Ajadi et al. (2009) reported that tramadol improved the quality of anaesthesia by increasing the duration of antinociception without increasing the duration of anaesthesia when co-administered with ketamine in pigs. These synergistic effects of ketamine and xylazine in enhancing the analgesic properties of tramadol have also been reported (Maksimović & Lutvikadić, 2021). Donatia et al. (2021) reported meta analysis evaluated comparative effect of tramadol combination with other opoids in perioperative or postoperative pain management without any mention of pentazocine. This study therefore evaluated the comparative effect of preemptive tramadol and pentazocine administration as preemptive analgesics on quality of anaesthesia in dogs undergoing ventral midline laparotomy surgical procedures.

MATERIALS AND METHODS

EXPERIMENTAL ANIMALS

Ten apparently healthy adult female Nigerian indigenous dogs weighing between 9kg-11kg were randomly allocated to two experimental groups of 5 bitches each. Following standard surgical procedure and techniques, all the dogs in group 1 and 2 either underwent gastrotomy or ovariohysterectomy. This research was approved (FUNAAB/COLVET/CREC/2023/10/05) by the Research and Ethics Committee of the college of veterinary medicine, Federal University of Agriculture, Abeokuta Ogun State.

EXPERIMENTAL DESIGN

Group 1 (PEN) received 2mg/kg pentazocine HCl while group 2 (TRAM) was administered with 2mg/kg Tramadol HCl intramuscularly fifteen minutes before administration of premedicants. Both groups were premedicated with 0.04mg/kg atropine sulphate intramuscularly and 1mg/kg 2% Xylazine hydrochloride (Xylased, Bioveta, Ivanovice, Czech Republic). About 7-10minutes after administration of premedicants, general anaesthesia was induced in both groups with 0.25 mg/kg of 1% diazepam (Bleorpam, Norris Medicine Ltd, Gujarat India) and 10 mg/kg of 5% ketamine (Ketamine hydrochloride, Rotexmedica, Trittau, Germany) intramuscularly. The anaesthetic agents in each group were injected simultaneously. Linear infiltration of 5mls of 2% Lidocaine hydrochloride (Labcalin® Laborate Pharmaceutical, India) was done to achieve incisional analgesia. Anaesthesia was maintained in both groups with half initial dose of induction agent as intravenous bolus

PHYSIOLOGICAL PARAMETERS

Baseline readings of heart rates (HR), Rectal Temperatures (RT) and respiratory rates (RR) of dogs were obtained at 0 minute before anaesthetic induction. The parameters were measured at 10, 20, 30, 40, 50, 60, 70, 80 and 90 minutes post anaesthetic induction. Pulse rate, respiratory rate and rectal temperature were determined using digital palpation, abdominal excursion and clinical thermometer respectively.

ANAESTHETIC PARAMETERS

The following anaesthetic parameters were determined following standard procedure

Onset of immobilization (OI): Duration between time of administration of premedicant to loss of wrighting reflex

Onset of anaesthesia (OA): Duration between time of administration of induction agent to loss of pedal withdrawal reflex

Duration of antinociception: Duration from complete loss of pedal withdrawal reflex to complete return of pedal withdrawal reflex.

Time to return of pedal reflex (TRPR): Time from end of anaesthetic drug administration to the animal gaining pedal withdrawal reflex

Time to sternal: time from return of pedal reflex to balance on sternal recumbency

Time to standing: Time from animal balancing on sternal recumbency to the animal going on standing posture.

Number of maintenance boluses: Total number of intravenous boluses administered

DATA ANALYSIS

All data were expressed as Mean ± Standard deviation. The cardiopulmonary and anesthetic data were compared between the groups using independent sample T-test on SPSS (Statistics Package for the Social Sciences, version 25;

SPSS Inc., Chicago, IL, USA). Values of $P \leq 0.05$ were considered significant.

RESULTS

PHYSISOLOGICAL PARAMETERS

Gastrotomy and ovariohysterectomy was successfully done in all dogs in group 1 and 2 and they all had a smooth recovery from anesthesia. The rectal temperature (Fig I) was significantly higher ($P<0.05$) in the tramadol group compared to the pentazocine group. In the pentazocine group the rectal temperature decrease non-significantly ($p>0.05$) from baseline throughout the duration of anesthesia. However, in the tramadol group, the rectal temperature decreases from the baseline to 30minutes into anesthesia and then increase gradually till the end of the anesthesia. From 60 minutes post anaesthetic induction, the rectal temperature increased significantly ($P<0.05$) till the end of the anaesthesia in the tramadol group compared to pentazocine group. Throughout the procedure, there was no significant difference ($P>0.05$) in the pulse rate (Fig II) between the two groups. However, the pulse rate in the pentazocine group was higher than tramadol group and increased or decreased haphazardly in both group throughout the anaesthetic period. The respiratory rate (Fig III) was higher in the tramadol group compared to the pentazocine although not significant ($p>0.05$). However, there was statistically significant difference between the initial respiratory rate of tramadol group compared to the pentazocine group.

ANAESTHETIC PARAMTERS

As shown in Table I, the meantime of standing was significantly higher ($p<0.05$) in the tramadol (33.80±10.71min) than in the pentazocine group (7.00±4.36min). However, there was no statistically significant ($P > 0.05$) difference in the other anaesthetic parameters between tramadol and pentazocine group. The mean onset of immobilization was shorter in tramadol group (5.20±2.86min) compared to pentazocine group (8.00±4.12min) and duration of antinociception was longer in tramadol group (48.00±5.08min) compared to pentazocine group (40.20±5.17min) while onset of anaesthesia, time to return of pedal withdrawal reflex and time to sternal was longer in tramadol group (22.40±16.53min, 11.40±16.13min, 25.80±14.52min) compared to pentazocine group (19.00±2.00min, 10.60±8.73min, 18.20±10.62min). The animals in tramadol groups (3.40±1.95) received less amount of maintenance bolus compared to the pentazocine group (4.20±2.17).

DISCUSSION

The administration of preemptive analgesia with either tramadol or pentazocine prior to premedication with xylazine-atropine and induction of anaesthesia with ketamine-diazepam combination in this study provided quality of anesthesia, good duration of analgesia as well as smooth recovery without untoward side effects on the cardiopulmonary indices of all the dogs that underwent ventral midline laparotomy surgery (ovariohysterectomy or gastrotomy). Surgical patients are believed to suffer less to no pain during general anesthesia but nociceptive signals that are continually generated during the procedure predispose the patient to higher risk of awareness, short anaesthetic and analgesic duration (Shanthanna et al., 2021). The addition of a preemptive analgesia in anaesthetic protocol prior to surgery has been reported to help alleviate these risks, thereby enhancing anaesthetic and analgesic qualities (Xuan et al., 2022; Kissin, 2000).

Pedal withdrawal reflex, a form withdrawal response due to artery forcep applied at the interdigital space to assess presence or absence of obnoxious stimulus and depth of anaesthesia is commonly used in surgery and has been used in several species of animals including rabbit (Murison 2008), pig (Ajadi *et al.*, 2009) and dogs (Khojasteh & Vesal, 2023). In this study, the pedal withdrawal response was absent in both groups after induction of anaesthesia and throughout the duration of anaesthesia. This is probably due to the inclusion of tramadol or pentazocine in anaesthetic protocol of both groups which have 3-6hours of duration of

TABLE I: The Mean ± SD of anaesthetic parameters recorded from Pentazocine or tramadol premedicated dogs undergoing surgical procedures.

Anaesthetic variables	Group	Mean±SD	P-value
Onset of immobilization (Min)	PEN	8.00±4.12	0.252
	TRAM	5.20±2.86	
Onset of anaesthesia (Min)	PEN	19.00±2.00	0.671
	TRAM	22.40±16.53	
Duration of antinociception (Min)	PEN	40.20±5.17	0.183
	TRAM	48.00±5.08	
Time to return of pedal reflex (Min)	PEN	10.60±8.73	0.925
	TRAM	11.40±16.13	
Time to sternal (Min)	PEN	18.20±10.62	0.375
	TRAM	25.80±14.52	
Time to standing (Min)	PEN	7.00±4.36	0.001*
	TRAM	33.80±10.71	
Number of maintenance boluses	PEN	4.20±2.17	0.557
	TRAM	3.40±1.95	

*Value is significant at $p<0.05$

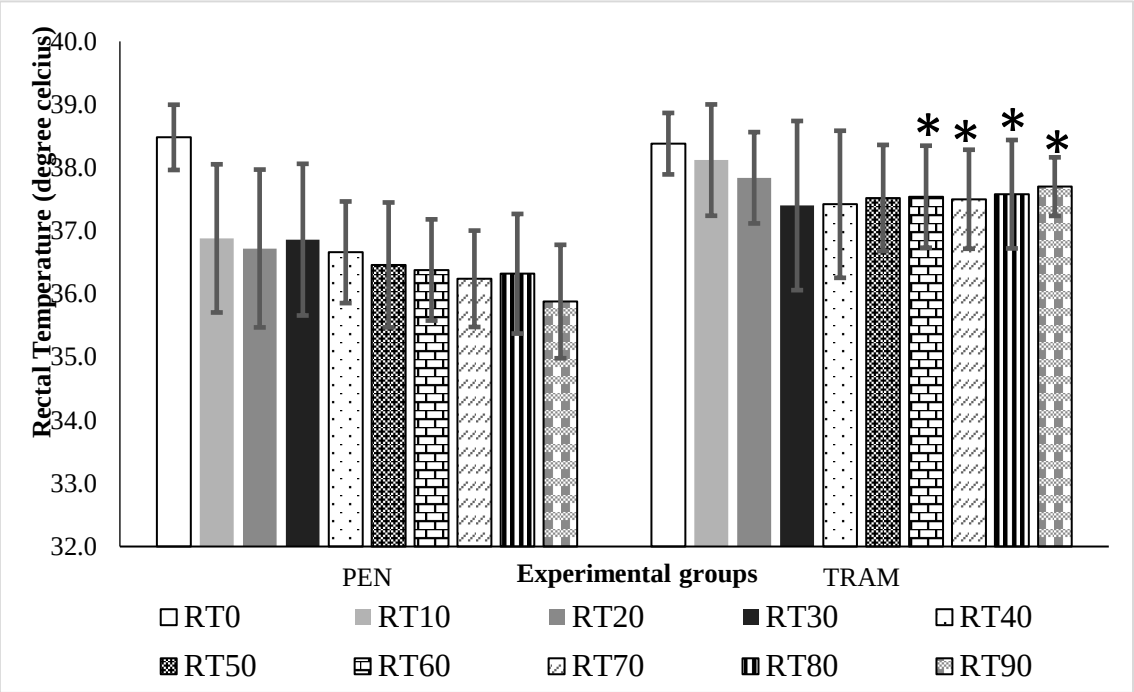

Figure I: The Mean±SD of rectal temperature obtained following pentazocine (PEN) or tramadol (TRAM) premedication in dogs undergoing surgical procedure. **Indicates statistically significant at p<0.05*

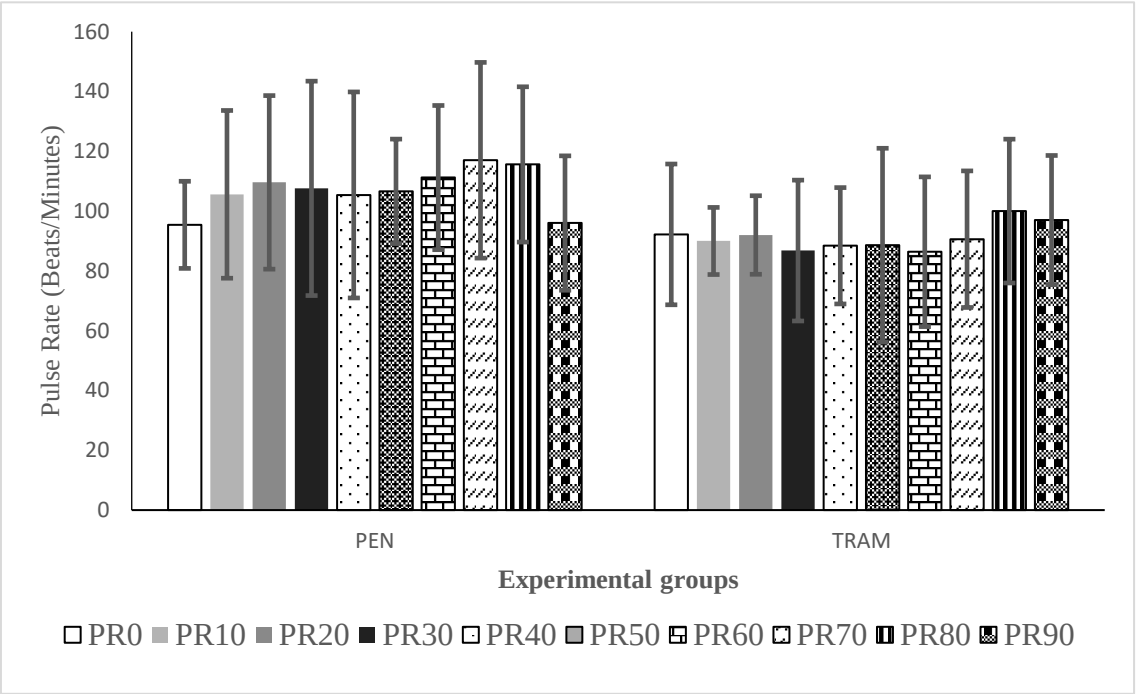

Figure II: The Mean±SD of pulse rate obtained following pentazocine (PEN) or tramadol (TRAM) premedication in dogs undergoing surgical procedure

analgesia (Donatia *et al.*, 2021) thereby resulting in lower nociceptive threshold within the surgery period. Previous report has shown that inclusion of opoid such as tramadol improve efficacy of anaesthesia and analgesia in animals (Ajadi et al., 2009).

However, tramadol produces an insifgnificantly ($p>0.05$) longer duration of antinociception compared to pentazocine. This was further stressed by the fact that animals in pentazocine group

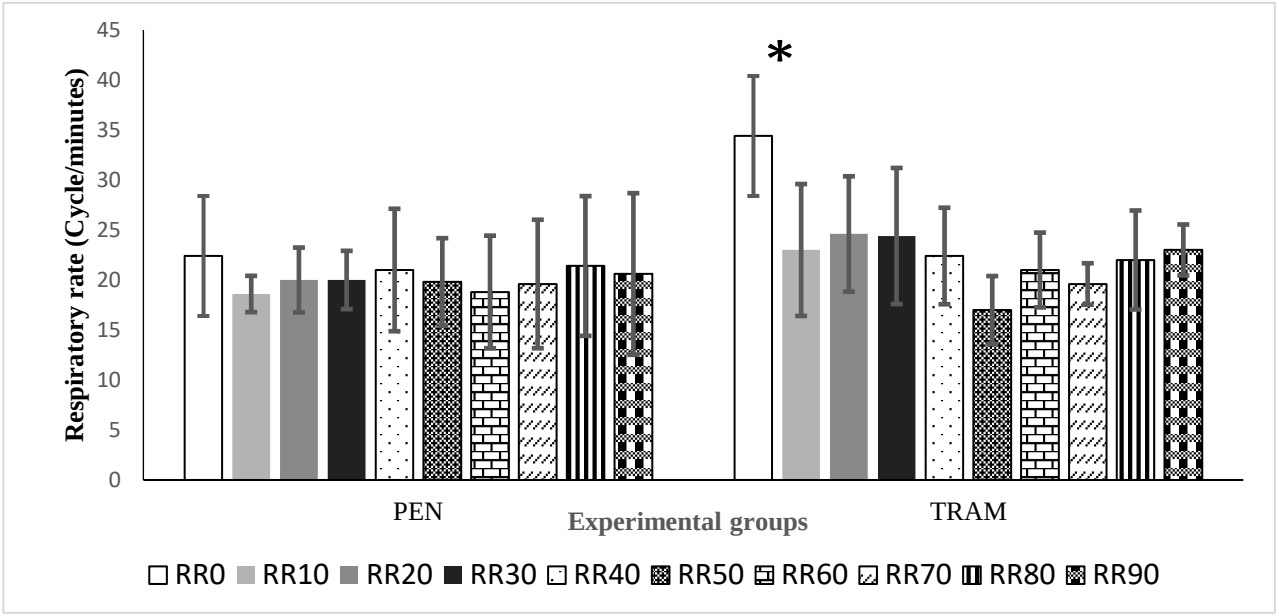

Figure III: The Mean±SD of respiratory rate obtained following pentazocine (PEN) or tramadol (TRAM) premedication in dogs undergoing surgical procedure. *Indicates statistically significant at $p<0.05$

required higher amount of maintenance bolus compared to tramadol group. Even though both tramadol and pentazocine have similar time of return of pedal withdrawal reflex. However, the overall duration of anaesthesia and analgesia is longer in tramadol group than the pentazocine group. Moreover, tramadol has been reported to have higher analgesic and antinociceptive effects than pentazocine in dogs undergoing ovariohysterectomy (Chaithra *et al.,* 2022; Chaithra *et al.,* 2024) and in human (Bano *et al.,* 2021). Some studies have reported that combination of ketamine-xylazine-and tramadol give the tramadol a superior analgesic effect seen (Maksimović and Lutvikadić, 2021). This is because tramadol has been reported to offers a better therapeutic analgesia when co-administered with other drugs rather than monotherapy (Domínguez-Oliva *et al.,* 2021). However, the addition of same protocol in the pentazocine group remove such bias and validate the superior preemptive analgesic effect of tramadol over pentazocine, just as observed by other researchers.

The combination of alpha 2-agonists with opoids, ketamine, diazepam, propofol and isoflurane particularly in dogs provides balanced anaesthesia that ensure sedation, muscle relaxation and analgesia (Lamont et al. 2012). Anaesthesia induced by xylazine combination with ketamine and opoids produces a safe state of anaesthesia in terms of physiological parameters (*Silva et al.,* 2010).

The cardiopulmonary parameters measured in this study were not significantly affected by the addition of either tramadol or pentazocine to the anaesthetic protocol. In both groups, there was no significant difference in the mean pulse rate throughout the period of monitoring. Immediately after administration of xylazine and atropine at 10min, the pulse rate in the pentazocine group increased and continued to increase insignificantly ($p> 0.05$) till 20 minutes before the animals got out of anaesthesia. However, the pulse rate in the tramadol group was lower than the pentazocine group even though it was not different from the baseline. The changes observed in the pulse rate of bothgroups might be due to presence of xylazine and the vagolytic effect of atropine (Borges *et al.* 2008). Diazepam decreases only respiratory rates but not heart rates unlike ketamine combinations with alpha 2 agonists (Longley, 2008). Administration of alpha-agonists in dogs can produce normo- or hypotension and bradycardia followed by an initial state of hypertension (Webb et al. 2014; Kellihan et al. 2015). The result of this study suggested that administration of tramadol or pentazocine as preemptive analgesia does not have a significant cardiodepressant effect making it a valuable protocol that can be adopted.

Similar to this study, there was no clinically significant respiratory depression in dogs following administration of opoids with ketamine-xylazine (Natalini*et al.,* 2007). Although the baseline respiratory rate was significantly higher than the respiratory rate taken after administration of premedicant and anaesthetic induction. This could have been due to the addition of the xylazine reportedly causing decreased respiratory rate in dogs (Changmin *et al.,* 2010). Moreso insignificant decrease respiratory rate following administration of tramadol or pentazocine has been reported in dogs (Chaithra *et al.,* 2022). In this study, there was decrease in rectal temperature in both groups. Hypothermia in general anaesthesia could be due to generalized blood redistribution through peripheral vasodilation, depression of thermoregulatory center, decreased metabolic rate and lower

skeletal muscle activity. There is a significant correlation between antinociception and hypothermia in beagle dogs administered opoid (KuKanich *et al.,* 2024). However, in this study, tramadol group with higher antinociception had significantly higher temperature compare to the pentazocine group. In dogs, opioids interfere with the thermoregulatory mechanism in the central nervous system resulting in decreases in body temperature (Monteiro *et al.,* 2008). The decrease in body temperature after administration of tramadol and pentazocine in dogs have been previously reported (Chaithra *et al.,* 2022)

CONCLUSION

In conclusion, the use of tramadol or pentazocine as preemptive analgesia in dogs anaesthetized with xylazine-ketamine-diazepam provided a rapid onset of action, smooth induction and recovery, good antinoceiception effect as well as minimal alterations in cardiopulmonary parameters which are within acceptable physiological limit. Even though tramadol provide longer duration of antinociception, pentazocine is an alternative replacement in dogs undergoing laparotomy especially in developing countries where there is limited access to tramadol.

REFERENCES

Ajadi, R. A., Olusa, T.A., Smith, O.F., Ajibola, E.S., Adeleye, O.E., Adenubi, O.T. & Makinde, F.A. (2009). Tramadol improved the efficacy of ketamine–xylazine anaesthesia in young pigs. *Veterinary Anaesthesia and Analgesia,* 36(6), 562-566.

Alexander, J.C., Patel, B. & Joshi, G.P. (2019). Perioperative use of pioids: Current controversies and concerns. *Best Practice in Research and Clinical Anaesthesiology,* 33,341–351

Bano, B., Bai, K., Jumani, S., Bashir, N., Mohsin, H. & Laghari, S. (2021). Effectiveness of tramadol compared to pentazocine in pain management during labour. *International Journal of Community Medicine and Public Health,* 8,4216-4220.

Borges, P.A., Nunes, N., Barbosa, V.F., Conceicao, E.D.V., Nishimori, C.T.D., Paula, D.P., Carareto, R., Thiesen, R. & Santos, P.A.C. (2008). Cardiorespiratory variables, bispectral index and recovery of anesthesia in dogs anesthetized with isoflurane, treated or not with tramadol. *Arqive Brasilian Medicina Veterinary and Zoologia*, 60(3), 613-619.

Brown, E.N., Pavone, K.J. & Naranjo, M. (2018). Multimodal general anesthesia: Theory and practice.
Anesthesia and analgesia, 127,1246–1258

Chaithra, S.N., Saikia, B. Konwar, B., Bayan, H., Devi1, T.R., Das, C. J. & Zorinpuii, H. (2024). Comparative studies on haemato-biochemical changes following pre-emptive analgesia with tramadol, pentazocine lactate and meloxicam in pain management of canine ovariohysterectomy *Indian Journal of Animal Sciences,* 94(2), 123–130,

Chaithra, S.N., Saikia, B., Konwar, B., Bayan, H., Sarma, K., Lallianchhunga, M.C. & Arya, R.S. (2022). Evaluation of Tramadol, Pentazocine Lactate and Meloxicam as Pre-emptive Analgesics for Pain Management in Canine Ovariohysterectomy. *Indian Journal of Animal Research,* 56(6), 695-703.

Changmin, H., Jianguo C, Dongming L, Guohong L. & Mingxing D (2010). Effects of xylazine alone and in combination with ketamine on the metabolic and neurohumoral responses in healthy dogs. *Veterinary Anaesthesia and Analgesia,* 37, 322–328

Cividjian, A., Petitjeans, F., Liu, N., Ghignone, M., de Kock, M. & Quintin, L. (2017). Do we feel pain during anesthesia?: A critical review on surgery-evoked circulatory changes and pain perception. *Best Practice in Research and Clinical Anaesthesiology,* 31, 445–67

Coutinho, A. J., Gasser, B., Rodriguez, M. G. K., Uscategui, A. A. R., Santos, V. J. C., Tiosso, C. de F., Barros, F. F. P. da C. & Toniollo, G. H. (2018). Comparison between single port videolaparoscopy and miniceliotomy with snook hot ovariohysterectomy techniques in bitches. *Ciênca Rural journal* 48(10), e20180345.

Dilip, C.R.S., Shetty, A.P., Subramanian, B., Kanna, R.M. & Rajasekaran, S. (2019). A prospective randomized study to analyze the efficacy of balanced pre-emptive analgesia in spine surgery. *Spine Journal*, 19, 569–577.

Domínguez-Oliva, A., Casas-Alvarado, A., Miranda-Cortés, A. E. & Hernández-Avalos I. (2021). Clinical pharmacology of tramadol and tapentadol, and their therapeutic efficacy in different models of acute and chronic pain in dogs and cats. *Journal Of Advanced Veterinary And Animal Research,* 8(3), 404-422

Donatia, P. A., Tarragonaa, L., Francob, J. V. A., Kreila, V., Fravegac, R., Diaza, A., Verdiera, N. & Oteroa P. E. (2021). Efficacy of tramadol for postoperative pain management in dogs: systematic review and meta-analysis. *Veterinary Anaesthesia and Analgesia,* 48, 283-296

Dunkman, W.J. (2018). Manning, M.W. Enhanced Recovery after Surgery and Multimodal Strategies for Analgesia. *Surgery Clinic of North America*, 98, 1171–1184.

Edwards, D.A., Hedrick, T.L., Jayaram, J., Argoff, C., Gulur, P., Holubar, S.D., Gan, T.J., Mythen, M.G., Miller, T.E. & Shaw, A.D. (2019). American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Perioperative Management of Patients on Preoperative Opioid Therapy. *Anesthesia and Analgesia,* 129, 553–566.

Egan, T.D. & Svensen, C.H. (2018). Multimodal general anesthesia: A principled approach to producing the drug-induced, reversible coma of anesthesia. *Anesthesia and Analgesia,* 127, 1104–1106

Egan, T.D. (2019). Are opioids indispensable for general anaesthesia? *British Journal of Anaesthesiology,* 122, e127–135.

Haffner, M., Saiz, A.M., Nathe, R., Hwang, J., Migdal, C., Klineberg, E. & Roberto, R. (2019). Preoperative multimodal analgesia decreases 24-hour postoperative

narcotic consumption in elective spinal fusion patients. *Spine Journal,* 19, 1753–1763.

Hernández-Avalos, I., Flores-Gasca, E., Mota-Rojas, D., Casas-Alvarado, A., Miranda-Cortés, A.E. & Domínguez-Oliva, A. (2021). Neurobiology of anesthetic-surgical stress and induced behavioral changes in dogs and cats: a review. *Veterinary World,* 14(2), 393–404

Hyland, S.J., Brockhaus, K.K., Vincent, W.R., Spence, N.Z., Lucki, M.M., Howkins, M.J. & Cleary, R.K. (2021). Perioperative Pain Management and Opioid Stewardship: A Practical Guide. *Healthcare* 9, 333.

Kaye, A.D., Urman, R.D., Rappaport, Y., Siddaiah, H., Cornett, E.M., Belani, K., Salinas, O.J. & Fox, C.J. (2019). Multimodal analgesia as an essential part of enhanced recovery protocols in the ambulatory settings. *Journal of Anaesthesiology and Clinical Pharmacology*, 35, S40–S45.

Kellihan, H.B., Stepien, R.L., Hassen, K.M. & Smith, L.J. (2015). Sedative and echocardiographic effects of dexmedetominine combined with butorphanol in healthy dogs. *Journal of Veterinary Cardiology*, 17, 282–292

Khojasteh, K. & Vesal, N. (2023). Comparison of propofol infusion rate required to abolish swallowing or pedal withdrawal reflexes in dogs. *Veterinary Research Forum*, 14(2), 79-85

Kissin, I. (2000). Preemptive analgesia. *Anesthesiology*, 93,1138e43

KuKanich, B. (2019). Pain management in veterinary species. In; Pharmacotherapeutics for veterinary dispensing. Wiley Blackwell, Hoboken, NJ, 173–88,

KuKanich, B., KuKanich, K., Tzic, A. D. C. & Anderson, E. E. (2024). Correlation of opioid antinociception and hypothermia in dogs-An animal welfare refinement. *Journal of veterinary pharmacology and therapeutics*, *47*(2), 73–79.

Lamont, L.A., Burton, S.A., Caines, D. & Troncy, E.D.V. (2012). Effects of 2 different infusion rates of medetomidine on sedation score, cardiopulmonary parameters, and serum levels of medetomidine in healthy dogs. *The Canadian Journal of Veterinary Research*, 76, 308–316.

Longley, L.A. (2008). Anaesthesia of Exotic Pets, Elsevier Saunders, London. Pp 47

Maksimović, A. & Lutvikadić, I. (2021). Efficiency of epidurally injected lidocaine, lidocaine and morphine or lidocaine and tramadol for postoperative analgesia in dogs following orchiectomy and ovariohysterectomy. *International Journal of Veterinary Science*, 10(1),13–18.

McEvoy, M.D., Scott, M.J., Gordon, D.B., Grant, S.A., Thacker, J.K., Wu, C.L., Gan, T.J., Mythen, M.G., Shaw, A.D. & Miller, T.E. (2017). American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) joint consensus statement on optimal analgesia within an enhanced recovery pathway for colorectal surgery: Part 1—From the preoperative period to PACU. *Perioperative Medicine* 6, 1–13.

Monteiro, E.R., Figueroa, C.D.N. & Choma J.C. (2008). Effects of methadone, alone or in combination with acepromazine or xylazine, on sedation and physiologic values in dogs. *Veterinary Anaesthesia and Analgesia*, 35, 519-527

Natalini, C.C., Polydoro, A.S. & Crosignani, N. (2007). Effects of morphine or tramadol on thiopental anesthetic induction dosage and physiologic variables in halothane anesthetized dogs. *Acta Scientiae Veterinariae.* 35, 161-166.

Nazifi, S., Shojaee, T.A., Mohammadi, S., Erjaee, H. & Mirzaie, A. (2019). The effect of tramadol and meloxicam, alone and in combination on oxidative stress status in dogs. *Comparative Clinical Pathology*, 28(4),1055–1060

Sadafule, N.N. & Karhade, S.S. 2018). Comparative study of efficacy of preoperative nalbuphine hydrochloride and pentazocine lactate on hemodynamic response to tracheal intubation and postoperative analgesia. *Anesthesia Essays Research*, 12, 218-222.

Shanthanna, H., Ladha, K. S. Kehlet, H. & Joshi, G. P. (2021). Perioperative Opioid Administration: A Critical Review of Opioid-free *versus* Opioid-sparing Approaches *Anesthesiology,* 134,645–59

Silva, F.C., Hatschbach, E., De Carvalho, Y.K., Minto, B.W., Massone, F. & Junior, P.N. (2010). Hemodynamics and bispectral index (BIS) of dogs anesthetized with midazolam and ketamine associated with medetomidine or dexmedetomidine and submitted to ovariohysterectomy. *Acta Cirurgia Brasileira*, 25, 181–189

Vadivelu, N., Chang, D., Helander, E.M., Bordelon, G.J., Kai, A. & Kaye, A.D. (2017). Ketorolac, oxymorphone, tapentadol, and tramadol. A comprehensive review. *Anesthesiology Clinics*, 35(2),e1–20

Vasiljević, M., Ristanović, D., Jovanović M., Davitkov, D., Bošnjak, I., Krstić, V. & Stanimirović, Z. (2015). Comparative analysis of parameters of intraoperative and postoperative pain in bitches undergoing laparoscopic or conventional ovariectomy. *Acta Veterinaria-Beograd*. 65(4), 488–495.

Webb, J.A., Rosati, M., Naigamwalla, D.Z. & Defarges, A. (2014): The use of the medetomidine-based sedation protocols to perform urohydropropulsion and cystoscopy in the dog. *The Canadian Veterinary Journal* 55, 1213–1218.

Xuan, C., Yan W, Wang D, Li, C., Ma, H., Mueller, A., Chin, V., Houle, T. T. & Wang, J. (2022). Efficacy of preemptive analgesia treatments for the management of postoperative pain: a network meta-analysis. British Journal of Anaesthesia, 129 (6), 946e958