Antinociceptive effect of lidocaine, tramadol, and their combination for lumbosacral epidural analgesia in rabbits undergoing experimental knee surgery

Mohamed Salem, Awad Rizk, Esam Mosbah, Adel Zaghloul, Gamal Karrouf and Marwa Abass*

Abstract

Aim: The current study aimed to evaluate the antinociceptive effect of lidocaine, tramadol, and their combination for lumbosacral epidural analgesia in rabbits undergoing knee surgery.

Materials and methods: This study was performed on 24 male New Zealand white rabbits weighing 2.8 to 3.0 kg and was allocated into three groups. All groups were anaesthetized by intramuscular (IM) injection of 35 mg/kg ketamine and 5 mg/kg xylazine, 0.1 mg/kg butorphanol. Rabbits in Group A received epidural analgesia of 4 mg/kg lidocaine 2%; Group B rabbits received epidural analgesia of 4 mg/kg tramadol 5%, and Group C rabbits received epidural analgesia of a combination of 4 mg/kg lidocaine and 4 mg/kg tramadol. Prior to and during surgery, the following parameters were recorded in a regular pre-set time interval: onset time of analgesia (OT), duration of flaccid paralysis (DFP), duration of analgesia (DA), onset and duration of sensory blockade, onset and duration of motor blockade, heart rate (HR), respiratory rate (RR), and rectal temperature (RT).

Results: The mean OT demonstrated a significant decrease ($P < 0.05$) in Group C (46.5 ± 1.4 sec) compared to Group A and B (61.0 ± 2.4 and 54.5 ± 3.5 sec), respectively. DFP was significantly lower ($P < 0.05$) in Group C (35.5 ± 2.9 min) than in Group A and B (17.6 ± 1.4 and 21.8 ± 3.6), respectively. DA showed a significant increase ($P < 0.05$) in group C (45.8 ± 3.3 min) compared to groups A and B, respectively (23.3 ± 1.1 and 31.5 ± 2.3). Heart rate, RR, and RT significantly decreased in Group C compared to the other groups.

Conclusion: According to the current study findings, lumbosacral epidural administration of lidocaine combined with tramadol could be a better choice for potentiating the analgesia than administration of either drug separately and may be safely used in rabbits undergoing knee surgery.

Keywords: Lumbosacral, Lidocaine, Tramadol, Ketamine, Rabbits

Background

Due to its proximity to the spinal cord receptors responsible for the modulation and transmission of nociceptive signals, lumbosacral analgesia is an effective method of analgesia [1, 2]. Lidocaine HCl is the most commonly used anesthetic agent administrated for epidural analgesia that is characterized by a rapid onset of action and effective desensitization [3]. Since the duration of...
Results

The mean OT was significantly decreased ($P<0.05$) in Group C (46.5 $\pm$ 1.4 seconds) compared to groups A and B, with values of (61.0 $\pm$ 2.4 and 54.5 $\pm$ 3.5 seconds), respectively. The mean DFP was significantly increased ($P<0.05$) in Group C (35.5 $\pm$ 2.9 minutes) compared to groups Group A and B, with means of (17.6 $\pm$ 1.4 and 21.8 $\pm$ 3.6 minutes) respectively. The mean DA was significantly increased ($P<0.05$) in Group C (45.8 $\pm$ 3.3 minutes) compared to Group A and B (23.3 $\pm$ 1.1 and 31.5 $\pm$ 2.3 minutes), respectively. Mean sensory blockade onset was significantly decreased in Group C (1.1 $\pm$ 0.1 minutes) compared to groups A and B, with values of (1.5 $\pm$ 0.4 and 1.6 $\pm$ 0.3 minutes) respectively. The mean time to the maximum sensory blockade was significantly decreased in Group C (3.1 $\pm$ 0.3 minutes) compared to groups A and B (3.6 $\pm$ 0.6 and 3.7 $\pm$ 0.3 minutes), respectively. The mean duration of sensory blockade was significantly increased ($P<0.05$) in group C (57.8 $\pm$ 1.7 minutes) compared to groups A and B, with values of (54.2 $\pm$ 1.2 and 54.1 $\pm$ 1.2 minutes), respectively (Table 1).

The mean motor blockage onset time was significantly decreased in Group C to reach (1.1 $\pm$ 0.1 minutes) compared to groups A and B, which have (1.8 $\pm$ 0.3 and 1.6 $\pm$ 0.3 minutes) respectively. Group C had a significantly shorter mean time to maximum motor blockade (2.60 $\pm$ 2.4 minutes) than groups A and B, which had (3.5 $\pm$ 0.4 and 3.5 $\pm$ 0.5 minutes) respectively. The mean duration of motor blockade was significantly increased ($P<0.05$) in group C (37.0 $\pm$ 1.8 minutes).

Table 1 The mean ± standard deviation of onset time (OT) (sec), duration of flaccid paresis (DFP) (min), duration of analgesia (DA) (min), sensory blockade onset (min), time to maximum sensory blockade (min), duration of sensory blockade (min), motor blockade onset (min), and time to maximum motor blockade (min) in rabbits. Group A: lidocaine epidural, Group B: tramadol epidural, and Group C: lidocaine- tramadol epidural.

| Parameters                                      | Group A (Lidocaine) | Group B (Tramadol) | Group C (Lidocaine and Tramadol) |
|-------------------------------------------------|---------------------|--------------------|----------------------------------|
| Onset time (OT) (sec)                           | 62.8 ± 3.3 a        | 54.5 ± 3.5 b,c     | 46.5 ± 1.4 c                    |
| Duration of flaccid paresis (DFP) (min)         | 17.6 ± 1.4 a        | 21.8 ± 3.6 b,c     | 35.5 ± 2.9 c                    |
| Duration of analgesia (DA) (min)                | 23.3 ± 1.1 a        | 31.5 ± 2.3 b,c     | 45.8 ± 3.3 c                    |
| Sensory blockade onset (min)                     | 1.5 ± 0.4 a         | 1.6 ± 0.3 a        | 1.0 ± 0.1 b,c                   |
| Time to maximum sensory blockade (min)          | 3.6 ± 0.6 a         | 3.7 ± 0.3 a        | 3.1 ± 0.3 a                     |
| Duration of sensory blockade (min)              | 54.2 ± 1.2 a        | 54.1 ± 1.2 a       | 57.8 ± 1.7 b,c                  |
| Motor blockade onset (min)                       | 1.8 ± 0.3 a         | 1.6 ± 0.2 a        | 1.1 ± 0.1 b,c                   |
| Time to maximum motor blockade (min)            | 3.5 ± 0.4 a         | 3.5 ± 0.5 a        | 2.6 ± 0.2 b,c                   |
| Duration of motor blockade (min)                | 31.7 ± 1.6 a        | 30.5 ± 2.9 a       | 37.0 ± 1.8 b,c                  |

Means with different superscript litters are significantly different at $P<0.05$

All within interaction, Wilks’ Lambda, $P<0.0001$; Within time, Wilks’ Lambda, $P<0.0001$; Time * groups, Wilks’ Lambda, $P<0.0001$
Table 2 The mean ± standard deviation of HR (beat/ min), RR (breath/ min) and RT (°C) measured at different times 10 minutes prior- and 10, 20, 30, 45, 60, 75, and 90 minutes post- the epidural analgesia in rabbits. Group A: lidocaine epidural, group B: tramadol epidural, and group C: lidocaine-tramadol epidural.

| Variables | Groups | Monitoring time (minutes) |
|-----------|--------|---------------------------|
|           |        | –10 | 10 | 20 | 30 | 45 | 60 | 75 | 90 |
| HR (beat/min) | A | 1440 ± 0.4 a | 1420 ± 0.5 a | 1346 ± 0.5 b | 1320 ± 0.6 b | 1245 ± 0.8 b | 1240 ± 0.6 b | 1275 ± 0.8 b | 1375 ± 0.8 b |
|            | B | 1440 ± 0.4 a | 1430 ± 0.6 a | 1408 ± 0.8 b | 1310 ± 0.8 a | 1277 ± 0.5 a | 1230 ± 0.8 b | 1273 ± 0.8 b | 1355 ± 0.8 a |
|            | C | 1450 ± 1.5 a | 1280 ± 0.9 b | 1153 ± 0.8 b | 1080 ± 1.1 b | 1070 ± 1.4 c | 1037 ± 0.5 c | 1227 ± 0.8 b | 1313 ± 0.8 c |
| RR (breath/min) | A | 60.0 ± 0.6 a | 55.7 ± 0.8 a | 51.5 ± 0.5 b | 48.2 ± 0.7 a | 47.3 ± 0.8 a | 49.7 ± 0.7 a | 53.2 ± 0.8 b | 597 ± 1.0 a |
|            | B | 60.2 ± 0.9 a | 57.0 ± 0.6 a | 54.3 ± 0.8 b | 45.8 ± 0.7 b | 44.3 ± 0.8 ab | 44.3 ± 0.8 c | 48.0 ± 0.6 c | 598 ± 1.4 a |
|            | C | 59.5 ± 0.8 a | 52.0 ± 1.9 b | 46.0 ± 0.9 c | 43.3 ± 0.8 c | 41.0 ± 0.9 b | 37.0 ± 0.6 c | 34.3 ± 0.8 c | 43.3 ± 0.8 b |
| RT °C | A | 39.4 ± 0.08 a | 39.3 ± 0.05 a | 39.2 ± 0.09 a | 38.4 ± 0.08 *b | 38.4 ± 0.06 b | 38.3 ± 0.05 b | 39.0 ± 0.05 ab | 39.2 ± 0.05 h b |
|            | B | 39.5 ± 0.07 a | 39.4 ± 0.05 b | 39.2 ± 0.05 a | 38.6 ± 0.08 b | 38.4 ± 0.05 b | 38.3 ± 0.05 b | 39.0 ± 0.05 b | 39.3 ± 0.04 b |
|            | C | 39.5 ± 0.07 a | 39.1 ± 0.05 b | 38.2 ± 0.06 b | 37.5 ± 0.06 c | 37.2 ± 0.06 c | 37.2 ± 0.04 c | 37.7 ± 0.08 c | 38.8 ± 0.06 b |

Means with different superscript letters are significantly different at P<0.05 among groups.
Means with an asterisk (*) differ significantly (P<0.05) from baseline.
All within interaction, Wilks’ Lambda, P<0.001; Within time, Wilks’ Lambda, P<0.0001; Time * groups, Wilks’ Lambda, P<0.001.

compared to groups A and B, with values of (31.7 ± 1.6 and 30.5 ± 2.9 minutes) respectively.

The mean HR was significantly decreased in all groups (P<0.05) from baseline, with the lowest value recorded at 60 min postoperatively with the following values: (124.0 ± 0.6 vs. 144 ± 0.4 in Group A, 123.7 ± 0.8 vs. 144 ± 0.4 in Group B, and 103.7 ± 0.5 vs. 145 ± 1.5 beat per min in Group C). The mean RR was significantly decreased in groups A and B (P<0.05) from baseline (60±0.6), with the lowest value recorded at 60 min postoperatively to be 49.7 ± 0.7 and 44.3 ± 0.8 breaths per min, respectively. The mean RR was significantly decreased in Group C (P>0.05) from baseline (59.5 ± 0.8), with the lowest value recorded at 75 min postoperatively (34.3 ± 0.8 breaths per min). The mean RT was significantly decreased in all groups (P<0.05), with the lowest value recorded at 60 min postoperatively (38.3 ± 0.05 vs. 39.4 ± 0.08 °C in Group A, 37.2 ± 0.04 vs. 39.5 ± 0.07 °C in Group B, and 37.2 ± 0.04 vs. 39.5 ± 0.07 °C in Group C; Table 2).

Discussion

Although xylazine–ketamine anesthesia causes a state of unconsciousness and the animals do not experience pain, where the nociception may not be abolished entirely [3, 21]. While the clinical evaluation of adequate intraoperative antinociception may be difficult, increased HR, RR, and RT may be observed in anesthetized animals in response to extensive surgical stimulation [5]. Meanwhile, blocking these responses by increasing xylazine and ketamine doses could result in severe cardiorespiratory depression [3]. Consequently, the present study aimed to evaluate the efficacy of lidocaine, tramadol, and their combination in producing intraoperative antinociception and analgesia in the immediate postoperative period without inducing clinically significant changes in HR, RR, and RT.

Rabbits were used in the present study because many reports have revealed that rabbits are a good model for studying the epidural block technique and evaluating the sensory and motor loss under standardized experimental conditions [22, 23]. Epidural analgesia could be used in painful surgical procedures for intraoperative and postoperative analgesia as well as continuous pain relief, particularly in animals with chronic pain [18].

Induction of lumbosacral epidural analgesia in ferrets and rabbits is bearly identical to that of the technique described for dogs and cats, with the exception that at the time of entry into the epidural space, the definitive popping sensation is rarely detected when the inner arcuate ligament is punctured [18]. Tramadol has been used intravenously, resulting in prolonged analgesia without severe side effects in horses [24]. Herein, the mean onset time of analgesia was significantly shorter with lidocaine tramadol combination than in the other groups (P<0.05). Moreover, the duration of analgesia was longer with the lidocaine tramadol combination than in the other groups (P<0.05), indicating that adding tramadol to lidocaine accelerates and prolongs the onset of analgesia. Similar findings were reported in a previous study conducted on ruminants and donkeys [25, 26].

The mean duration of flaccid paralysis was significantly longer in the lidocaine tramadol combination group compared to the other groups (p<0.05). This finding can be attributed to a synergistic effect between lidocaine and tramadol. Combining the two drugs can decrease the side
effects of each individual drug and increase the duration of flaccid paralysis and analgesia [27].

Tramadol is an analgesic with central effects acting on opioid receptors and inhibiting the reuptake of norepinephrine and serotonin [13]. The mean duration of sensory and motor blockade was longer in the lidocaine tramadol combination group compared to the other groups ($p < 0.05$), which was also reported in Tavakoli’s study [18]. In groups A, B, and C, the mean HR, RR, and RT decreased significantly from baseline. In contrast to Atiba’s research [28], who reported that HR, RR, and RT were non-significance different from baseline values after epidural administration of lidocaine and tramadol alone or in combination in buffalo calves.

Conclusion
In conclusion, the findings of this study indicated that the combination of tramadol-lidocaine produced good analgesia with relatively rapid onset and increased duration of action compared to each drug alone. This combination may also be beneficial in the clinical practice for a longer duration in orthopedic surgery.

Materials and methods
Study sample
In this study, a total of 24 male New Zealand white rabbits weighing 2.8 to 3.0 kg were used in this study. The rabbits were kept in the animal house of Mansoura Veterinary Teaching Hospital, Faculty of Veterinary Medicine, Mansoura University, Egypt, for two weeks before starting the experiment. All animals had free access to food and water and were kept under standardized conditions. Animals were allowed to acclimatize to their cages and surroundings for several days. This study was approved by the Scientific Research Ethical Committee, Faculty of Veterinary Medicine, Mansoura University, Egypt Code No. Ph.D./15.

Study design
All rabbits received an intramuscular injection of xylazine HCl (Xylaject, 20 mg/ ml, ADWIA, Cairo, Egypt) at a dose of 5 mg/kg and ketamine HCl (Aneket®, 50 mg/ ml, NEON Laboratories Ltd., Mumbai, India) at the dose of 15 mg/kg. The technique of lumbosacral injection in rabbits is similar to that described in dogs [29]. The lumbosacral area was aseptically prepared. The hind limbs of the rabbits were flexed to allow the greatest opening of the lumbosacral space. The epidural injections were performed via 50 mm, 20-gauge needles. Before the injection, aspiration was used to ensure that the needle did not penetrate the blood vessels. The correct placement of the needle was confirmed by the hanging drop technique and lack of resistance during the injection. The rabbits were randomly allocated into three groups ($n = 8$) as follows:

- **Group A**: lumbosacral administration of 4 mg/kg of lidocaine (Debocaine, 20 mg/ ml, the Arab Company for Gelatin and Pharmaceutical industries, Cairo, Egypt).
- **Group B**: lumbosacral administration of 4 mg/kg tramadol (Minpharm, 50 mg/ mL, Grünenthal, Germany).
- **Group C**: lumbosacral administration of a combination of 4 mg/kg lidocaine HCL and 4 mg/kg tramadol.

Study design
The knee joint was aseptically prepared, and an anteromedial parapatellar incision was used to open the joint. Using an electric drill with a 3.5 mm diameter bit, an osteochondral defect of 5 mm depth and 4 mm width was created in the middle of the trochlear groove. The joint was flushed with sterile normal saline. The joint capsule was sutured using a 3–0 polyglycolic acid suture (EGYSORB, Taisier Med, Cairo, Egypt) with a simple continuous suture pattern. The subcutaneous tissues were closed using a subcuticular suture pattern using the same suture material, and the skin incision was closed using polypropylene 2/0 (PROLENE, ETHICON, USA). In all groups, the mean average duration of surgery was $15 \pm 1.1$ min.

Monitoring
The heart rate (HR) (beats/min) was recorded by auscultation using a stethoscope, respiratory rate (RR) (breath/ min) was documented by counting thoracic excursions, and the rectal temperature (RT) was documented using a digital temperature. These parameters were evaluated at $-10$, $10$, $20$, $30$, $45$, $60$, $75$, and $90$ minutes before and after lumbosacral drug administration.

The sensory blockade was recorded by observing an aversive reaction to pinprick stimulus with a needle (18-gauge) starting from the sacral to thoracic skin every minute for 5 minutes after lumbosacral injection and then every five minutes till the sensory blockade vanished. The motor activities were continuously recorded and assessed every 30 sec till reaching the motor blockade peak intensity and then evaluated every five minutes.

The lumbosacral epidural anesthetic indices were recorded for each rabbit according to [5, 18], which include:

- **Time to onset of analgesia (OT)**: Time that elapsed between injection of the drug and loss of response to pinprick.
- **Duration of flaccid paralysis (DFP)**: Time that elapsed between injecting the drug and rabbits becoming ambulatory.
Duration of analgesia (DA): Time that elapsed between injection of the drug and return of response to pinprick in the tail and both hind limbs.

The onset time of sensory blockade: Time between administration of the drug and the start of sensory blockade.

Duration of sensory blockade: A time interval during which the animal presented sensory blockade.

Time to maximum sensory blockade: Time between administering the drugs and reaching the maximum sensory blockade.

The onset time of motor blockade: Time that elapsed between administration of the drug and the start of motor blockade.

Duration of motor blockade: Time that the animal presented motor blockade.

Data analysis
The normality of qualitative values was assessed using normal probability plots and the Kolmogorov-Simonov test generated with the UNIVARIATE procedure of SAS. All experimental data are expressed as mean ± standard deviation (STD). A one-way analysis of variance (ANOVA) was used to analyze the data, followed by Tukey-Kramer HSD for multiple comparisons to assess the analgesic effect of lidocaine and tramadol. Statistical analyses were performed using a commercial program (JMP, version 5.0.1a). The level of statistical significance for all tests was set at $p \leq 0.05$.

Acknowledgments
The authors would like to thank the Department of Veterinary Surgery, Anesthesiology, and Radiology-Mansoura university staff for their assistance.

Authors’ contributions
Salem M, Rizk A, and Abbas M performed the experiments and drafted the paper. Mosbah E, Zaghloul A, and Karrouf G analyzed the data and contributed to the final revision and submission. All authors read and approved the final manuscript.

Funding
Open access funding provided by The Science, Technology & Innovation Funding Authority (STDF) in cooperation with The Egyptian Knowledge Bank (EKB). This study did not receive any funding.

Availability of data and materials
All data generated or analyzed during this study are included in this article.

Declarations
Ethics approval and consent to participate
All experiments were performed in accordance with relevant guidelines and regulations. The Welfare and Ethics Committee approved this study of the Faculty of Veterinary Medicine, Mansoura University, Egypt (Code No. Ph.D. 15). All procedures in this study were performed following ARRIVE guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare that there is no conflict of interest in the current research work.

Received: 10 May 2022   Accepted: 20 June 2022
Published online: 29 June 2022

References
1. Sibanda S, Hughes JL, Pawson PE, Kelly G, Bellenger CR. The effects of preoperative extradural bupivacaine and morphine on the stress response in dogs undergoing femoro-tibial joint surgery. Vet Anaesth Analg. 2006;33:246–57.
2. Troncy E, Junot S, Keroack S, Sammut V, Pibarat P, Genevois J-P, et al. Results of preemptive epidural administration of morphine with or without bupivacaine in dogs and cats undergoing surgery. 265 cases (1997–1999). J Am Vet Med Assoc. 2002;221:6666–72.
3. Antorczyk A, Lisda B, Skrzypczak P, Kielbowicz Z. Comparison of analgesia provided by lidocaine or morphine delivered epidurally in rabbits undergoing hindlimb orthopedic surgery. Pol J Vet Sci. 2019;22:31–5.
4. Rastabi H, Guranejnad S, Naddaf H, Hasani A. Comparison of the application of lidocaine, lidocaine-dexmethasone and lidocaine-epinephrine for caudal epidural anesthesia in cows. Iran J Vet Res. 2018;19:172.
5. Marjani M, Tavakoli A, Tavakoli J. Comparison of the Analgesic Effects of Lidocaine, Xylazine and their Combination Used into the Epidural Space in Rabbits. Iran J Vet Res. 2014;9:17–22.
6. Ragab G, Seif M, Halfaya FM. Comparison of tramadol, lidocaine and tramadol-lidocaine combination for epidural analgesia in goats. J Vet Med Res. 2017;24:124–31.
7. Zayed M, Mahmoud E, Khalil A, Salah M, Moustafa M, Youssf M, et al. Lumbosacral injection of lidocaine, detomidine and lidocaine–detomidine in goats: anti-nociceptive effects and changes on haematobiochemical parameters. J Appl Anim Res. 2020;48:57–62.
8. Pascoe PJ, Dyson D. Analgesia after lateral thoracotomy in dogs epidural morphine vs. intercostal bupivacaine. Vet Surg. 1993;22:141–7.
9. Steagall PV, Simon BT, Teixeira Neto FI, Luna SP. An update on drugs used for lumbosacral epidural analgesia and anesthesia in dogs. Front Vet Sci. 2017;4:688.
10. Azari O, Molaei MM, Roshani H. Caudal epidural analgesia using lidocaine alone and in combination with tramadol in dromedary camels. Iran J Vet Surg. 2014;9:27–32.
11. Gunduz M, Ozalevli M, Ozbek H, Ozcengiz D. Comparison of caudal ketamine with lidocaine or tramadol administration for postoperative analgesia of hypospadias surgery in children. Pediatr Anesth. 2006;16:158–63.
12. Senel AC, Ucikin O, Timurkaynak A. Does the addition of tramadol and ketamine to ropivacaine prolong the axillary brachial plexus block? Biomed Res Int. 2014;2014:686287.
13. Raffa RB, Friederichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an‘atypical’opioid analgesic. J Pharmacol Exp Ther. 1992;260:275–85.
14. Baniadam A, Afshar FS, Ahmadian F. Analgesic effects of tramadol hydrochloride administered via caudal epidural injection in healthy adult cattle. Am J Vet Res. 2010;71:20–5.
15. Dehkordi SH, Bgham-Sadegh A, Gerami R. Evaluation of anti-nociceptive effect of epidural tramadol, tramadol-lidocaine and lidocaine in goats. Vet Anaesth Analg. 2012;39:106–10.
16. Mastrocinque S, Almeida TF, Tatarunas AC, Imagawa VH, Otsuki DA, Materra JM, et al. Comparison of epidural and systemic tramadol for analgesia following ovariohysterectomy. J Am Anim Hosp Assoc. 2012;48:310–9.
17. DelRossi R, Módolo T, Maciel P, Pagliosa R. Efficacy of epidural lidocaine combined with tramadol or neostigmine on perineal analgesia in the horse. Equine Vet J. 2013;45:497–502.
18. Tavakoli A, Kazemi-Mehrjerdi H. Enhancing analgesic effects of lidocaine in rabbit epidural analgesia using metoclopramide or tramadol. Iran J Vet Sci Technol. 2011;3:41–8.
19. Hermeto LC, DeRossi R, Marquez BC, Jardim PH. Potentiation of epidural lidocaine by co-administering tramadol by either intramuscular or epidural route in cats. Can J Vet Res. 2015;79:214–20.
20. Amarpal X, Kinjavdekar P, Aithal H, Pawde A, Singh J, Udehiya R. Evaluation of xylazine, acepromazine and medetomidine with ketamine for general anaesthesia in rabbits. Scand J Lab Anim Sci. 2010;37:223–9.
21. Meylan N, Elia N, Lysakowski C, Tramer M. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. Br J Anaesth. 2009;102:156–67.
22. Johnston MS. Clinical approaches to analgesia in ferrets and rabbits: Elsevier; 2005. p. 229–35.
23. Malinovsky J-M, Bernard J-M, Baudrimont M, Dumand J-B, Lepage J-Y. A chronic model for experimental investigation of epidural anesthesia in the rabbit. Reg Anesth Pain Med. 1997;22:80–5.
24. Natalini CC, Robinson EP. Evaluation of the analgesic effects of epidurally administered morphine, alfentanil, butorphanol, tramadol, and US0488H in horses. Am J Vet Res Ismail. 2000;61:1579–86.
25. Ismail ZB. Epidural analgesia in cattle, buffalo, and camels. Vet World. 2016;9:1450.
26. Marzok MA, El-khodery SA. Comparative analgesic and sedative effects of tramadol, tramadol-lidocaine and lidocaine for caudal epidural analgesia in donkeys (Equus asinus). Vet Anaesth Analg. 2015;42:215–9.
27. Wang C, Chakrabarti MK, Whitwam JG. Specific enhancement by fentanyl of the effects of intrathecal bupivacaine on nociceptive afferent but not on sympathetic efferent pathways in dogs. J Am Soc Anesthesiol. 1993;79:766–73.
28. Atiba A, Ghazy A, Gomaa N, Kamal T, Shukry M. Evaluation of analgesic effect of caudal epidural tramadol, tramadol-lidocaine, and lidocaine in water buffalo calves (Bubalus bubalis). Vet. Med Int. 2015;2015.
29. Hamilton SM. The Analgesic Effects of Epidural Ketamine in Dogs With a Chemically Induced Synovitis: A Comparison Between Pre-or Post-Injury Administration. ETDs: Virginia Tech Electronic Theses and Dissertations. 2003.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.