The Journal of Veterinary Medical Science

NOTE

Surgery

Analgesic and cardiopulmonary effects of premedication with tramadol in calves anesthetized with the infusion of guaifenesin and thiamylal

Ahram KIM[1], Naoki SASAKI[2], Inhyung LEE[1], Kyuyoung LEE[3] and Jong-Pil SEO[4]*

[1]Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Seoul National University, Seoul 08826, Republic of Korea
[2]Department of Clinical Veterinary Science, Yamaguchi University, Yamaguchi 753-8515, Japan
[3]Center of Animal Disease Modelling and Surveillance, The Department of Medicine and Epidemiology, School of Veterinary Medicine University of California, Davis, CA 95616, USA
[4]College of Veterinary Medicine and Veterinary Medical Research Institute, Jeju National University, Jeju 63243, Republic of Korea

J. Vet. Med. Sci.
83(12): 1988–1993, 2021
doi: 10.1292/jvms.21-0196

Received: 2 April 2021
Accepted: 15 September 2021
Advanced Epub:
1 November 2021

ABSTRACT. This study examined the analgesic and cardiopulmonary effects of intravenous (IV) tramadol during general intravenous anesthesia in calves. Calves were premedicated with diazepam (0.2 mg/kg, IV) with tramadol (2 mg/kg, IV) (group T) or saline (group S). Anesthesia was induced by thiamylal sodium (4 mg/kg, IV) and maintained with an infusion (2 ml/kg/hr) of 5% guaifenesin containing thiamylal sodium (2 mg/ml). Additional thiamylal sodium (1–2 mg/kg, IV) was administered when interference from the calves was observed during surgery. The total counts of additional thiamylal sodium administration, analgesia score using a visual analog scale, recovery time, and cardiopulmonary function in the different groups were assessed and compared. Group T showed significantly fewer counts of additional drug administration and a significantly higher analgesia score. Tramadol may provide adequate analgesia with minimal cardiopulmonary changes in calves during general anesthesia.

KEY WORDS: analgesia, calf, pain, surgery, tramadol

General anesthesia, local anesthesia, sedation, and tranquilization are required in common bovine practice, including castration, cesarean section, claw amputation, umbilical hernia, and disbudding, which is regarded as a painful condition in cattle [1, 13, 16, 17]. Inhalation anesthesia may only be possible in an equipped hospital environment, but injectable anesthesia is used in the field easily without specific devices [18, 19]. Several types of calf injectable anesthetics are available, such as thiamylal sodium−guaifenesin combination and xylazine −ketamine combination [8]. In calves, diazepam can be used instead of xylazine to avoid the cardiovascular adverse effects of α_2-adrenergic agonists [10].

Pain management of livestock is becoming ethically important, and appropriate guidelines should be established during the surgical procedures [2]. Pain is better controlled through a combination of regional and systemic analgesics [6]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and local anesthetics are commonly administered to cattle to manage pain during the perioperative period [9]. Because pain control is also advantageous for animal welfare, effective pain management needs to target various mechanisms to cover all pain, such as NSAIDs and opioids [12]. The consumers' awareness of beef cattle welfare is growing [23], and the recognition and management of pain is an essential element of good animal welfare [20]. Appropriate analgesics, such as NSAIDs, opioids, and local anesthetics, are essential [6, 9, 10]. Many studies have emphasized the poor pain management of painful procedures in cattle [9]. In one study, a local anesthetic was administered for perioperative NSAIDs to manage pain in the feet of dairy cattle [4]. Effective pain management using various mechanisms, such as NSAIDs and opioids, is essential for welfare issues [12]. This study examined the use of analgesics in calves.

Tramadol is believed to induce analgesia via the μ-opioid and α_2-receptors with a low risk of substance dependence [14]. Recently, tramadol has shown potential opioid analgesic effects in horses and dogs [15, 22], and it is not a controlled drug in South Korea [22]. Although several studies have examined the effects of tramadol during the postoperative period in dogs undergoing

*Correspondence to: Seo, J.-P.: jpseo@jejunu.ac.kr

an ovariohysterectomy [15], few studies have evaluated the clinical responses to tramadol during general anesthesia in calves. Tramadol is a centrally acting opioid analgesic used to control moderate-severe pain in humans [21]. In cattle, tramadol has been used as epidural anesthesia in many studies [3, 5]. One study reported that intravenous tramadol reduced postoperative nociception in young calves after disbudding calves [7].

This study examined the analgesic and cardiopulmonary effects of tramadol and during general intravenous anesthesia in calves. Twelve Holstein male calves (average age four weeks, average weight 49.2 ± 5.8 kg) were used in this experiment. The Experimental Animal Committee of Obihiro University of Agriculture and Veterinary Medicine approved this randomized, blind, two-way crossover design study (Approval No. 24-2). Each calf used in the study was healthy based on a physical examination and laboratory tests, including a complete blood cell count and biochemical profile.

The calves were weighed and underwent a physical examination in the preparing room. Food and water were withheld for 2 to 4 hr before the experiment. A jugular vein was catheterized with an 18 or 20 G, 3.5-inch extended use catheter (BD Angiocath, BD Medical, Sandy, UT, USA) for drug administration and complete blood count analysis. The auricular artery was catheterized with a 22 G, 1.25-inch over-the-needle catheter (BD Angiocath, BD Medical) to measure the arterial blood pressure and sample the arterial blood. The arterial blood pressure was measured using a blood pressure transducer (Transpac IV Monitoring Kit, ICU Medical, San Clemente, CA, USA) positioned and zeroed at the heart level. The calves were equipped with electrocardiogram monitoring pads for the base-apex lead and rectal temperature for data collection.

All calves received intravenous diazepam (0.2 mg/kg, IV; Horizon, Astellas Pharma, Tokyo, Japan). Subsequently, tramadol (2 mg/kg, IV; Tramal, Nippon Shinyaku Co., Kyoto, Japan) (group T) or an equal volume of saline (group S) was administered to each of the six calves five min later. Anesthesia was induced by thiamylal sodium (4 mg/kg, IV; Isozole, Nichiiko Pharmaceutical, Toyama, Japan) five min later and was maintained with a combination of 500 ml of 5% guaifenesin (Guaifenesin, ALPS Pharmaceutical Industries, Gifu, Japan) and 1,000 mg of thiamylal sodium by constant rate infusion (2 mg/kg/hr) during surgery (Fig. 1). Additional thiamylal sodium (1 to 2 mg/kg, IV) was administered when any interference from the calves was observed during surgery. Oxygen (1 to 2 l/min) was supplied with a facemask to prevent hypoxemia. A 10 to 14 mm endotracheal tube was prepared in the case of an emergency.

During general anesthesia, all calves were subjected to a partial radial nerve neurectomy for another experiment to evaluate the nerve regeneration factors. The skin over the radial nerve was clipped and disinfected using 70% isopropyl alcohol and povidone-iodine scrub swabs on the right lateral recumbency. Local anesthesia with 10 ml of 2% lidocaine (Xylocaine Injection 2%, AstraZeneca, Osaka, Japan) was performed subcutaneously and intramuscularly as a line block at the surgical sites. The calves received a 3 cm long skin and muscle incision over the humerus. After exposing the radial nerve, the nerve was identified by electrical stimulation (1 mA, 30 Hz, 2 sec) using an electrical stimulator. (JM-1A, Wuxi Jiajian Medical Instrument, Inc., Wuxi, China). After 1 cm of radial nerve was resected, the incised muscle was closed with absorbable suture material (Vicryl # 2-0, Ethicon, Edinburgh, UK). The skin was sutured either with simple continuous or simple interrupted sutures (Prolene # 2-0, Ethicon).

The duration of anesthesia and recovery time, including the time to head up, time to sternal recumbency, and time to stand after finishing the last skin suture, were recorded. The analgesic effects of tramadol were assessed by comparing the administration count of additional thiamylal sodium between groups T and S.

In addition, the analgesic effects of tramadol were also assessed by comparing the analgesic score between groups. The analgesia score (AS) was assessed using a reversed-10 cm visual analog scale (VAS) at six time points; 10 cm represented complete analgesia, and 0 cm indicated a loss of analgesia. The VAS assessments considered spontaneous movements (struggling and flinching) and vocalization of the calves as a direct response to surgical manipulation: 1 to 2 cm when continuous flicking and paddling and vocalization were present, 3 to 4 cm when continuous flicking and struggling were present, 5 to 6 cm when moderate movement was present, 7~8 cm when mild movement was present, and 9 to 10 cm when there was barely any movement. The six-time points involved the main surgical manipulations: 1) local anesthetic injection, 2) skin and muscle incision, 3) approach and manipulation, 4) electrical stimulation, 5) neurectomy, and 6) skin and muscle closure. Two scorers blinded to the treatments recorded the AS at each time point.

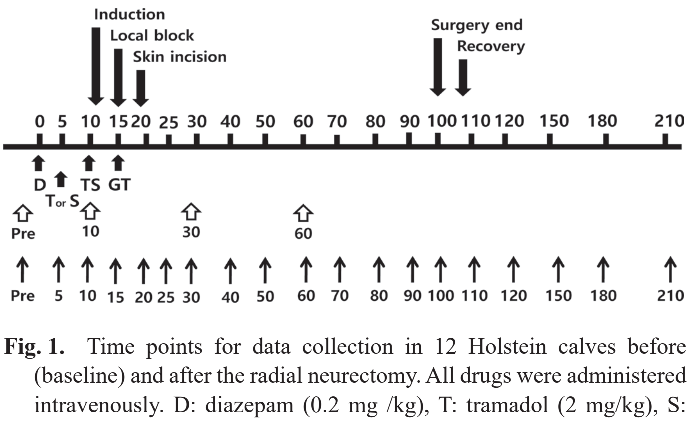

Fig. 1. Time points for data collection in 12 Holstein calves before (baseline) and after the radial neurectomy. All drugs were administered intravenously. D: diazepam (0.2 mg /kg), T: tramadol (2 mg/kg), S: 0.9% normal saline (2 mg/kg), GT: 5% guaifenesin (500 ml) + thiamylal sodium (1,000 mg) combination at a rate of 2 mg/kg/hr, TS: thiamylal sodium (2 mg/kg); ↑: minutes from the initial administration of the drugs and measure of the heart rate (HR), respiratory rate (RR), capillary refilling time (CRT), and rectal temperature (RT); white arrow⇧: minutes from the initial administration of drugs and complete blood test (CBC) and arterial blood gas analysis (ABGA).

To evaluate the cardiorespiratory function, heart rate (HR), respiratory rate (RR), body temperature (BT), arterial blood pressure, and capillary refilling time (CRT) were recorded at 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 180, and 210 min after the induction of anesthesia (Fig. 1). The HR, BT, systolic arterial pressure (SAP), mean arterial pressure (MAP), and diastolic arterial pressure (DAP) were recorded using a Colin BP-500 patient monitor (Nippon Colin, Tokyo, Japan). The RR was determined by the movement of the thorax and abdomen. The CRT was measured by pressing the calves' gums using the thumb for two seconds and observing the color change. Blood samples were collected at 0, 30, and 60 min after the induction of anesthesia and analyzed using a blood gas analyzer (Rapidlab 348, Bayer Medical Co., Tokyo, Japan) and a complete blood cell counter (Celltac α, Nihon Kohden, Tokyo, Japan).

The descriptive statistics are summarized as the mean ± standard deviation (SD). The statistically significant differences in recovery time and the total amount and count of the additional anesthetics were evaluated using a Wilcoxon rank-sum test. A linear mixed model, including the random effects of calves, was used to measure the statistical association of tramadol administration with the cardiopulmonary functions and AS of two examiners. The covariance error structure for repeated measures of an individual calf was selected using the Akaike information criterion (AIC), and the first-order auto-regressive matrix was finally selected. The statistical significance was accepted at $P<0.05$. All statistical analyses were performed on R (V 3.6.3) in R studio (V 1.1.447).

Group T required significantly fewer counts of additional thiamylal than group S (Fig. 2). Group T showed significantly higher AS for one to six stages than group S (Fig. 3). The recovery time, including the time to reach the sternal position and the time to reach the standing position from the end of the closure of the skin, were similar in the two groups. The MAP was significantly lower in the T group than the S group but within the normal reference values. The HR, RR, BT, CRT, SAP, and DAP were similar in the two groups throughout the experiment. The cardiopulmonary parameters (PaO_2, $PaCO_2$, HCO_3^-, SaO_2, PCV, and Hb) were similar and within the normal reference values. Eleven out of 12 calves recovered well from anesthesia. One of them died, and the autopsy revealed pulmonary edema and hemorrhage.

In the present study, tramadol was administrated preoperatively as premedication to provide preemptive analgesic effects during surgical procedures. Preemptive tramadol might help reduce pain throughout the surgical procedure because the total amount of additional thiamylal was significantly lower in group T than group S. Many studies reported that tranquilizers, sedatives, and analgesics decrease the requirement for subsequent anesthetic drugs [8]. The CRI of lidocaine reduced the isoflurane requirement during umbilical surgery in calves [24]. The CRI of detomidine reduced the halothane requirement in horses than with halothane alone [25]. In the present study, group T required less anesthetic drug and used a lower amount of additional anesthetics (Fig. 2). This suggests that the analgesic effects of tramadol may have helped reduce the additional injectable anesthetic agent.

The prolonged recovery times may have been associated with the relatively deep level of anesthesia maintained throughout the procedure [25]. On the other hand, the recovery time to standing from finishing the last skin suture was similar in the two groups in the present study. The mean recovery time was 315 ± 65 and 351 ± 143 min in groups T and S, respectively, but the recovery time from anesthesia was similar in the two groups.

The cardiovascular function was one of the indicators monitored to assess the degree of anesthesia [2, 24]. The HR is used as an indicator of pain in dehorning [11], but some studies showed that the administration of tramadol affects the blood pressure in calves. In the present study, increases in the HR and blood pressure at 20 min might have been caused by pain related to the skin

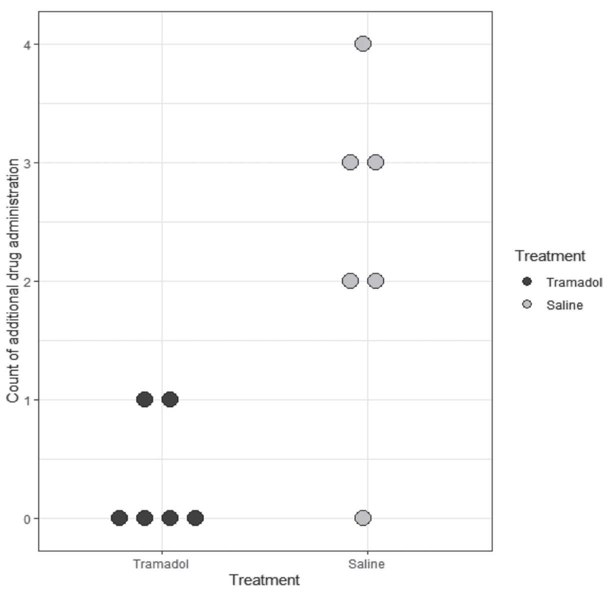

Fig. 2. Comparison of the additional thiamylal administration in groups T and S. The two groups showed a significant difference in the count of additional drug administration ($P<0.05$). Group T required fewer counts of additional IV administration of thiamylal than Group S.

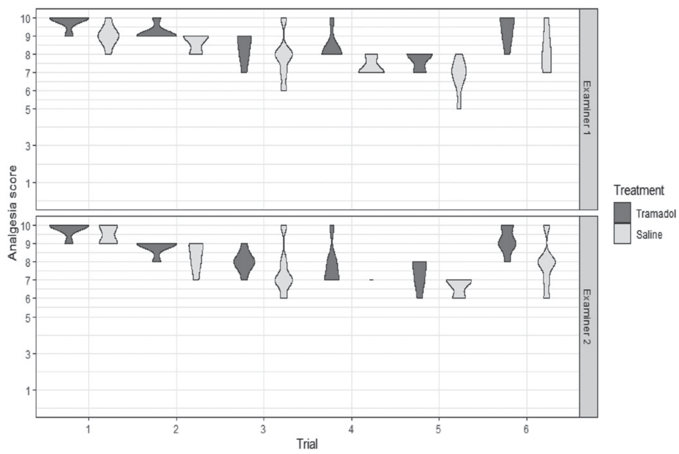

Fig. 3. Comparison of the analgesia score in groups T and S. The measurement of inter-rater reliability (Cohen's Kappa) based on the two approaches showed that two observers showed moderate agreement in the analgesia score. The data were analyzed in a linear mixed model, including the fixed effects. The covariance error structure with a first-order auto-regressive matrix was used to evaluate the repeated measures of an individual calf. The two groups showed a significant difference in the analgesia score. ($P<0.05$). Group T showed a significantly higher analgesia score than Group S. The mean ± SD in group T and S was 8.5 ± 0.5 and 7.8 ± 0.9, respectively.

incision in group S, whereas they were stable in group T (Fig. 4). The HR might have increased due to pain, and blood pressure is likely to rise simultaneously. In addition, the HR and blood pressure from 50 to 100 min for electrical stimulation, neurectomy, and skin closure were higher in group S than group T (Fig. 4). Group T showed a significantly lower MAP than group S. Managing pain might be related to the relative blood pressure in the control group. In addition, it might be related to the lower counts of the additional thiamylal administration in group T for adequate anesthesia management.

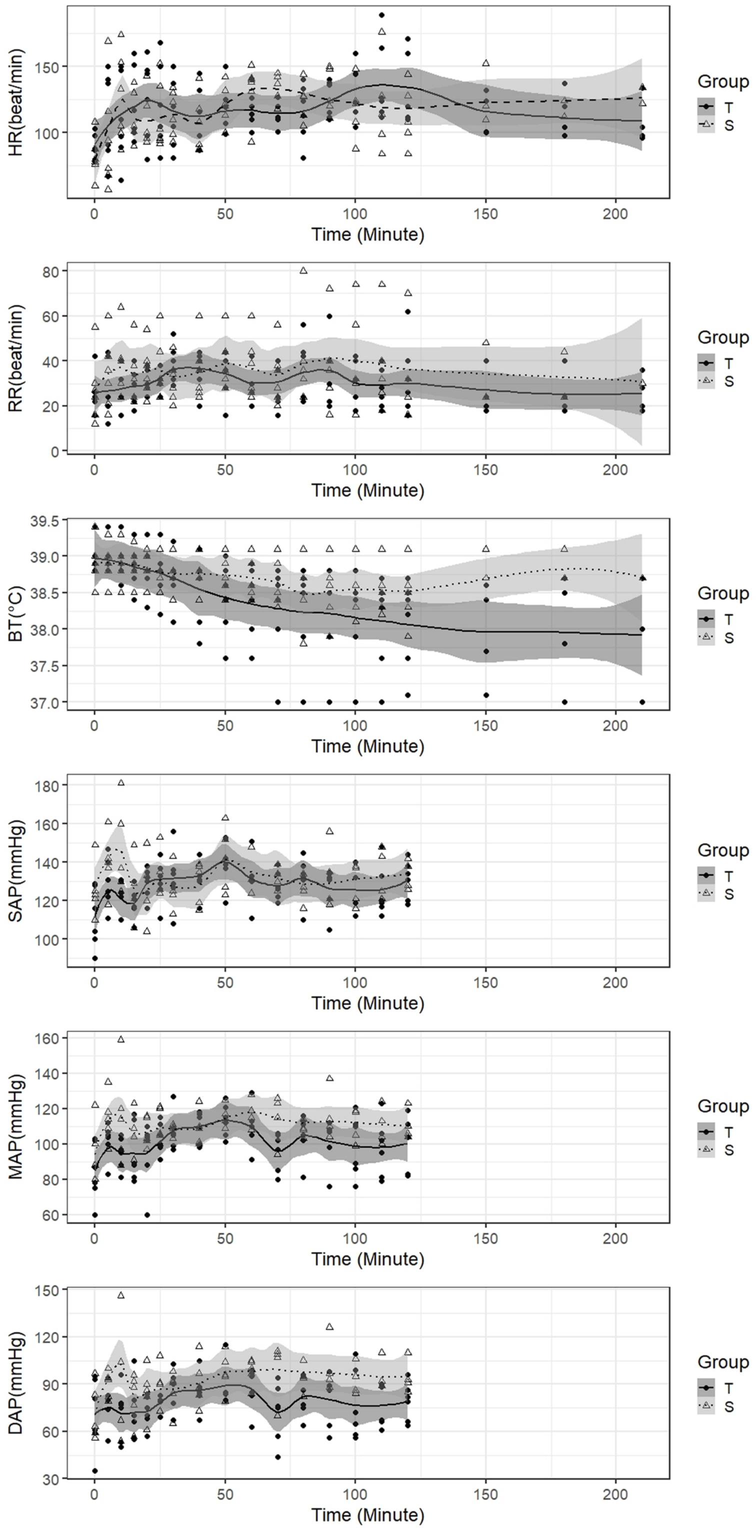

Fig. 4. Cardiopulmonary values in groups T and S. The mean arterial blood pressure (MAP) was significantly different (P<0.05). The other values were not significantly different. Solid line and dot: group T, Dash line and triangle: group S, Shadow: 95% confidence interval, asterisk: outlier.

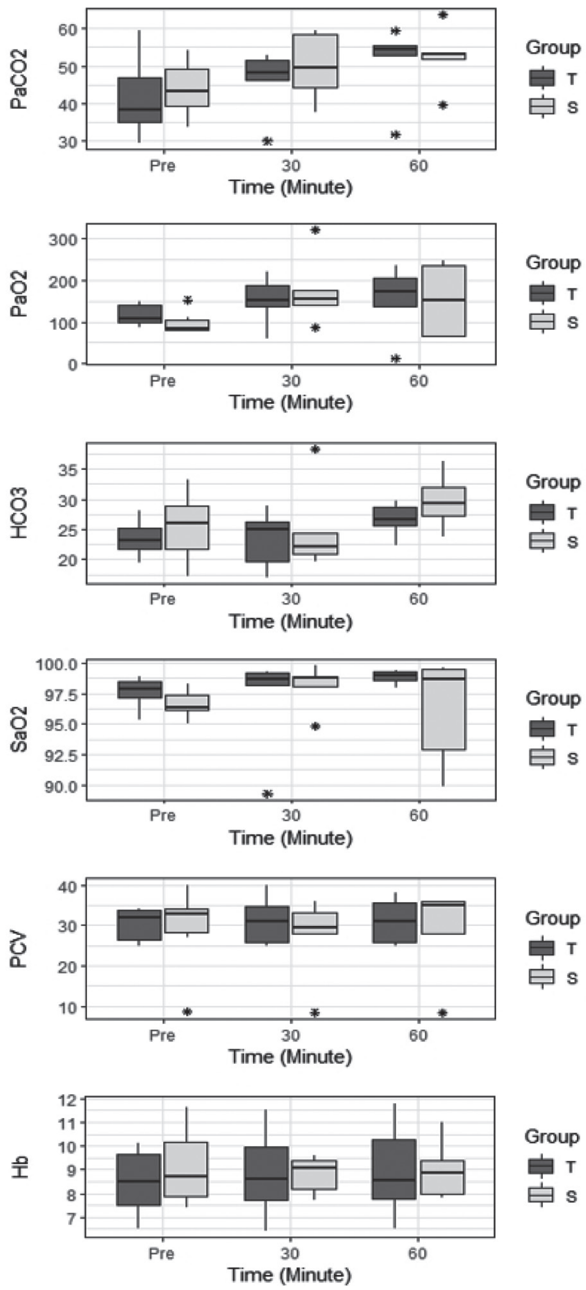

Fig. 4. Continued.

Because group T showed a significantly high AS, it might be effective pain control during a surgical procedure. On the other hand, it might also be associated with the dose of other additional anesthetics. Nevertheless, the estimate is uncertain because it might be related to the relatively different dose of other additional thiamylal for an individual.

One of the 12 calves died of respiratory failure during surgery; the autopsy revealed pulmonary edema and hemorrhage. This might be due to the idiopathic respiratory failure despite the endotracheal intubation in an emergency, and it is not due to the tramadol because the calf belonged to the control group.

In conclusion, tramadol showed analgesic activity with minimal differences in the cardiopulmonary function and reduced the additional amount of injectable anesthetics during the surgical procedure in calves. This suggests that preoperative intravenous tramadol may be helpful in general anesthesia for surgical procedures in calves.

CONFLICT OF INTEREST. The authors declare no financial or personal conflicts of interest.

ACKNOWLEDGMENT. The authors thank all veterinarian and staff who participated in this study.

REFERENCES

1. Al Noman, Z., Hasan, I., Arif, M., Ferdous, J., Sachi, S., Alam, M. R. and Sikder, M. H. 2018. Retrospective study of surgical cases of ruminants at Veterinary Teaching Hospital, Bangladesh Agricultural University. *J. Adv. Vet. Anim. Res.* **5**: 81–87. [CrossRef]
2. Anderson, D. E. and Edmondson, M. A. 2013. Prevention and management of surgical pain in cattle. *Vet. Clin. North Am. Food Anim. Pract.* **29**: 157–184. [Medline] [CrossRef]
3. Atiba, A., Ghazy, A., Gomaa, N., Kamal, T. and Shukry, M. 2015. Evaluation of analgesic effect of caudal epidural tramadol, tramadol-lidocaine, and lidocaine in water buffalo calves (Bubalus bubalis). *Vet. Med. Int.* **2015**: 575101. [Medline] [CrossRef]
4. Becker, J., Reist, M., Friedli, K., Strabel, D., Wüthrich, M. and Steiner, A. 2013. Current attitudes of bovine practitioners, claw-trimmers and farmers in Switzerland to pain and painful interventions in the feet in dairy cattle. *Vet. J.* **196**: 467–476. [Medline] [CrossRef]
5. Bigham, A. S., Habibian, S., Ghasemian, F. and Layeghi, S. 2010. Caudal epidural injection of lidocaine, tramadol, and lidocaine-tramadol for epidural anesthesia in cattle. *J. Vet. Pharmacol. Ther.* **33**: 439–443. [Medline] [CrossRef]
6. Bonnet, F. and Marret, E. 2007. Postoperative pain management and outcome after surgery. *Best Pract. Res. Clin. Anaesthesiol.* **21**: 99–107. [Medline] [CrossRef]
7. Braz, M., Carreira, M., Carolino, N., Rodrigues, T. and Stilwell, G. 2012. Effect of rectal or intravenous tramadol on the incidence of pain-related behaviour after disbudding calves with caustic paste. *Appl. Anim. Behav. Sci.* **136**: 20–25. [CrossRef]
8. Carroll, G. L. and Hartsfield, S. M. 1996. General anesthetic techniques in ruminants. *Vet. Clin. North Am. Food Anim. Pract.* **12**: 627–661. [Medline] [CrossRef]
9. Fajt, V. R., Wagner, S. A. and Norby, B. 2011. Analgesic drug administration and attitudes about analgesia in cattle among bovine practitioners in the United States. *J. Am. Vet. Med. Assoc.* **238**: 755–767. [Medline] [CrossRef]
10. Greene, S. A. 2003. Protocols for anesthesia of cattle. *Vet. Clin. North Am. Food Anim. Pract.* **19**: 679–693, vii. [Medline] [CrossRef]
11. Grøndahl-Nielsen, C., Simonsen, H. B., Lund, J. D. and Hesselholt, M. 1999. Behavioural, endocrine and cardiac responses in young calves undergoing dehorning without and with use of sedation and analgesia. *Vet. J.* **158**: 14–20. [Medline] [CrossRef]
12. Herskin, M. S. and Nielsen, B. H. 2018. Welfare effects of the use of a combination of local anesthesia and NSAID for disbudding analgesia in dairy calves-reviewed across different welfare concerns. *Front. Vet. Sci.* **5**: 117. [Medline] [CrossRef]
13. Huxley, J. N. and Whay, H. R. 2006. Current attitudes of cattle practitioners to pain and the use of analgesics in cattle. *Vet. Rec.* **159**: 662–668. [Medline] [CrossRef]
14. Ide, S., Minami, M., Ishihara, K., Uhl, G. R., Sora, I. and Ikeda, K. 2006. Mu opioid receptor-dependent and independent components in effects of tramadol. *Neuropharmacology* **51**: 651–658. [Medline] [CrossRef]
15. Kongara, K., Chambers, J. P. and Johnson, C. B. 2012. Effects of tramadol, morphine or their combination in dogs undergoing ovariohysterectomy on peri-operative electroencephalographic responses and post-operative pain. *N. Z. Vet. J.* **60**: 129–135. [Medline] [CrossRef]
16. Laven, R. A., Huxley, J. N., Whay, H. R. and Stafford, K. J. 2009. Results of a survey of attitudes of dairy veterinarians in New Zealand regarding painful procedures and conditions in cattle. *N. Z. Vet. J.* **57**: 215–220. [Medline] [CrossRef]
17. Lomax, S. and Windsor, P. A. 2013. Topical anesthesia mitigates the pain of castration in beef calves. *J. Anim. Sci.* **91**: 4945–4952. [Medline] [CrossRef]
18. Offinger, J., Meyer, H., Fischer, J., Kästner, S. B. R., Piechotta, M. and Rehage, J. 2012. Comparison of isoflurane inhalation anaesthesia, injection anaesthesia and high volume caudal epidural anaesthesia for umbilical surgery in calves; metabolic, endocrine and cardiopulmonary effects. *Vet. Anaesth. Analg.* **39**: 123–136. [Medline] [CrossRef]
19. Picavet, M. T. J. E., Gasthuys, F. M. R., Laevens, H. H. and Watts, S. A. 2004. Cardiopulmonary effects of combined xylazine-guaiphenesin-ketamine infusion and extradural (inter-coccygeal lidocaine) anaesthesia in calves. *Vet. Anaesth. Analg.* **31**: 11–19. [Medline] [CrossRef]
20. Rutherford, K. M. D. 2002. Assessing pain in animals. *Anim. Welf.* **11**: 31–53.
21. Scott, L. J. and Perry, C. M. 2000. Tramadol: a review of its use in perioperative pain. *Drugs* **60**: 139–176. [Medline] [CrossRef]
22. Seo, J. P., Son, W. G., Gang, S. and Lee, I. 2011. Sedative and analgesic effects of intravenous xylazine and tramadol on horses. *J. Vet. Sci.* **12**: 281–286. [Medline] [CrossRef]
23. Tucker, C. B., Coetzee, J. F., Stookey, J. M., Thomson, D. U., Grandin, T. and Schwartzkopf-Genswein, K. S. 2015. Beef cattle welfare in the USA: identification of priorities for future research. *Anim. Health Res. Rev.* **16**: 107–124. [Medline] [CrossRef]
24. Vesal, N., Spadavecchia, C., Steiner, A., Kirscher, F. and Levionnois, O. L. 2011. Evaluation of the isoflurane-sparing effects of lidocaine infusion during umbilical surgery in calves. *Vet. Anaesth. Analg.* **38**: 451–460. [Medline] [CrossRef]
25. Wagner, A. E., Dunlop, C. I., Heath, R. B., Turner, A. S. and Trotter, G. W. 1992. Hemodynamic function during neurectomy in halothane-anesthetized horses with or without constant dose detomidine infusion. *Vet. Surg.* **21**: 248–255. [Medline] [CrossRef]