

## Analgesic effect of caudal epidural ketamine in cattle

Inhyung Lee\*, Tomo Yoshiuchi<sup>1</sup>, Norio Yamagishi<sup>2</sup>, Kenji Oboshi<sup>2</sup>, Yu Ayukawa, Naoki Sasaki and Haruo Yamada

Department of Clinical Veterinary Science, Obihiro University of Agriculture and Veterinary Medicine, Inada, Obihiro, Hokkaido 080-8555, Japan

<sup>1</sup>Prevention of Epidemics Section, Kenou Animal Hygiene Service Center of Tochigi Prefecture, Hiraide, Utsunomiya, Tochigi 321-0905, Japan

<sup>2</sup>Research Center for Animal Hygiene and Food Safety, Obihiro University of Agriculture and Veterinary Medicine, Inada, Obihiro, Hokkaido 080-8555, Japan

**This study was performed to clarify the analgesic effect of ketamine injected into the first intercocygeal (Co1-Co2) epidural space in standing cattle. Five adult cows were randomly received 3 treatments at least 1 week interval: 5, 10 and 20 mL of 5% ketamine. Sedation, analgesia, ataxia and other effects on cardiopulmonary and rumen functions were assessed before ketamine administration and until 120 min. The analgesia without sedation was shown at tail and perineum about 5 min after all three treatments. The duration of analgesia was significantly increased according to the volume of ketamine ( $p < 0.01$ ). There was a similar tendency of ataxia with individual variation. There were minimal effects on cardiopulmonary and rumen functions. The present study showed that caudal epidural ketamine administration induced analgesia without sedation in cows, and the duration of analgesia was dose dependent with ataxia. However, the duration of analgesia after 5 and 10 mL ketamine administration is short for common surgical procedures and pain relief of perineum. Further studies are needed to prolong the duration of analgesia without side effects.**

**Key words:** caudal epidural anesthesia, ketamine, analgesia, cattle

### Introduction

Caudal epidural anesthesia is simple and inexpensive, and requires no sophisticated equipment [22]. It is routinely used in ruminants for obstetric manipulations, caudal surgical procedures, and as an adjunct treatment for

control of rectal tenesmus [17]. Local anesthetics, such as lidocaine, and  $\alpha_2$ -adrenergic agonists, such as xylazine and medetomidine, have been used independently [15,22], and combinations of these drugs provide rapid onset and a longer duration of analgesia [9,23]. Although many experimental and clinical studies mainly focused on analgesic effect of administered drugs [3-5,9,20,21,23], there are side effects such as cardiopulmonary and ruminal depression, and ataxia.

Ketamine, a potent noncompetitive antagonist at N-methyl-D-aspartate (NMDA) receptors in the spinal cord, has been used as a general anesthetic or analgesic in clinic [1,11,16,24]. Gomez De Segura *et al.* [8] reported that epidurally administered ketamine in the horse produces local spinal and central nervous system effects with analgesia and sedation but minimal cardiopulmonary effects. To author's knowledge, there are few studies that have investigated the effects of ketamine after caudal epidural administration in adult cattle. This study was performed to clarify the analgesic effect of ketamine injected into the first intercocygeal (Co1-Co2) epidural space in standing cattle.

### Materials and Methods

The protocol and experimental design were approved by the Obihiro University of Agriculture and Veterinary Medicine Laboratory Animal Care and Use Committee. Five 2- to 4-year-old Holstein cows (mean  $\pm$  SD,  $3.2 \pm 0.8$  years), weighing  $478 \pm 60$  kg with body condition score (BCS) value  $2.50 \pm 0.40$  [7], were used in this study.

Cows were restrained in a chute. The skin area over the first intercocygeal (Co1-Co2) space was identified and aseptically prepared [10,22]. Epidural puncture was performed with an 18-gauge, 38 mm needle, that directed at right angle to the general contour of the croup, and correct needle placement in the epidural space was confirmed by

\*Corresponding author

Phone: +81-155-49-5379; Fax: +81-155-49-5379

E-mail: DOL825@hotmail.com

hanging-drop method and noting no resistance during solution injection [10,22]. Each cow randomly received 3 treatments at least 1 week interval: 5, 10 and 20 mL of 5% ketamine hydrochloride (Ketalar, Sankyo Co., Tokyo, Japan). The ketamine solution was administered at a rate of 0.5 mL/sec with the bevel directed cranially.

Sedation, analgesia and ataxia were assessed before ketamine administration and at 5 min intervals until 60 min and at 15 min intervals thereafter until 120 min. Sedation was defined when the upper eyelids drooped, the degree of the head position against the shoulder and the animal's reduced awareness of its surroundings [15]. The analgesia in the tail, perineum, hindlimbs and flank were assessed by the responses to superficial and deep muscular pinpricks. Ataxia was assessed by observing the hindlimb position, swaying and leaning against the chute or any knuckling of the fetlocks of the hindlimbs [4,15].

Heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP), rumen motility (RM) and rectal temperature (RT) were assessed before ketamine administration and at 15 min intervals thereafter until 120 min. A standard axis-base electrocardiogram (DynaScope 3400, Fukuda Denshi, Tokyo, Japan) was monitored continuously to detect HR and arrhythmias during the experiment. RR was determined by counting thorax and abdominal excursions during 1 minute. MAP was measured by placing a catheter with pressure transducer (MK6030US Monitor kit, Baxter, Tokyo, Japan) in auricular artery of ear. RM was evaluated by auscultation of the left paralumbar fossa and determination of the rate of ruminal contractions during 2 consecutive minutes. RT was measured by electrical thermometer per rectum.

Descriptive statistics (mean  $\pm$  SD) was used, and one-way ANOVA and Bonferroni/Dunn tests were utilized to compare the time of onset and duration of analgesia (mean of left and right sides) between the three groups. Values for HR, RR, MAP, RM and RT were analyzed by using repeated measures ANOVA. A value of  $p < 0.05$  was considered significant.

## Results

There was no sedative effect in all three doses of ketamine administration. The onset of analgesia was almost similar in all three treatments (Table 1). The main analgesic areas in 5 and 10 mL treatments were tail and perineum, but analgesia of upper hindlimbs was shown after 20 mL treatment. The duration of analgesia was significantly increased according to the volume of ketamine ( $p < 0.01$ ) (Table 1). Ataxia was not observed after 5 mL treatment, but four cows after 10 mL treatment showed slight ataxia. After 20 mL treatment, all five cows showed ataxia with individual variation. Ataxia of two cows was slight and other two cows showed moderate, and

**Table 1.** Analgesic and ataxic effects of ketamine after caudal epidural administration in cows (min)

Ketamine (mL)	Analgesia		Ataxia	
	Onset	Duration	Onset	Duration
5 (n=5)	6.5 $\pm$ 2.2 (n=5)	17.0 $\pm$ 6.7 (n=5)		
10 (n=5)	5.0 $\pm$ 0.0 (n=5)	34.0 $\pm$ 7.6* (n=5)	6.3 $\pm$ 2.5 (n=4)	30.0 $\pm$ 23.8 (n=4)
20 (n=5)	5.0 $\pm$ 0.0 (n=5)	62.5 $\pm$ 8.7† (n=5)	11.0 $\pm$ 8.9 (n=5)	48.0 $\pm$ 17.9 (n=5)

\*:  $p < 0.01$  versus 5 mL treatment group, †:  $p < 0.0001$  and  $p < 0.001$  versus 5 and 10 mL treatment group, respectively

one cow was recumbent. There was no significant difference in the onset and duration of ataxia (Table 1).

Although HR showed some significant changes after 10 and 20 mL administration (Table 2), these are within normal ranges. RR, MAP, RM and RT did not show any changes during experiments (Table 2).

## Discussion

This study showed that caudal epidural ketamine administration induced analgesia without sedation in cows, and the area and duration of analgesia were dose dependent like as in horses [8]. Although there were no significant effects on cardiopulmonary and rumen functions at any dose, ataxia was dose dependent.

Ketamine is known to have activity as a local analgesic, and NMDA antagonist, an opioid agonist/antagonist and, possibly, as an antimuscarinic [10,11]. Differences in the analgesic response to epidurally administered ketamine have been observed; attributable to anatomic differences, dose regimen, and inhalation anesthesia [17]. These complex actions and differences in analgesic response have made the evaluation of epidural ketamine difficult [10] and the epidural analgesic effect of ketamine remain controversial [1].

Several factors may influence both the extent and the area involved by epidurally administered drugs [18,22]. Especially intrinsic anatomic factors may play an important role in determining epidural spread [13]. In preliminary study, we examined the cranial distribution of new methylene blue (NMB) solution injected into the Co1-Co2 epidural space in adult cows. Five mL NMB solution administered to eight adult cows distributed until lumbosacral region. This was greater than the common number of dermatomes of bilateral analgesia after administration of lidocaine [9] and ketamine in this study. This means that there is a wider distribution of solution in the epidural space than indicated by dermatomal analgesia [12,13]. Because ketamine has similar pharmacologic

**Table 2.** Cardiopulmonary and other effects of ketamine after caudal epidural administration in cows

	Ketamine (mL)	Time (min)								
		0	15	30	45	60	75	90	105	120
HR (per min)	5	48 ± 10	49 ± 12	52 ± 11	47 ± 10	52 ± 10	51 ± 14	49 ± 10	51 ± 11	51 ± 12
	10	47 ± 8	50 ± 10	54 ± 3*	54 ± 12	52 ± 10	51 ± 5	50 ± 9	50 ± 10	51 ± 9
	20	53 ± 8	56 ± 10	56 ± 8	57 ± 10	59 ± 8	61 ± 7*	60 ± 11	60 ± 13	57 ± 10
RR (per min)	5	32 ± 10	35 ± 11	34 ± 12	35 ± 11	30 ± 7	34 ± 12	35 ± 9	35 ± 11	35 ± 12
	10	30 ± 7	32 ± 11	35 ± 11	32 ± 5	34 ± 11	34 ± 11	32 ± 10	34 ± 10	32 ± 11
	20	32 ± 17	35 ± 18	35 ± 18	35 ± 19	32 ± 17	32 ± 17	36 ± 20	34 ± 16	34 ± 16
MAP (mm Hg)	5	108 ± 5	106 ± 2	105 ± 9	105 ± 6	105 ± 5	111 ± 8	106 ± 7	107 ± 8	108 ± 9
	10	111 ± 12	109 ± 10	110 ± 17	108 ± 9	109 ± 13	121 ± 11	111 ± 13	107 ± 13	110 ± 11
	20	120 ± 16	116 ± 11	112 ± 7	111 ± 13	108 ± 15	105 ± 13	112 ± 16	111 ± 10	111 ± 11
RM (per 2 min)	5	3.2 ± 0.4	3.2 ± 0.4	3.4 ± 0.5	3.2 ± 0.4	3.8 ± 0.4	3.2 ± 0.4	3.2 ± 0.4	3.6 ± 0.5	3.0 ± 0.0
	10	3.0 ± 0.0	3.2 ± 0.4	3.0 ± 0.0	3.2 ± 0.4	3.5 ± 0.5	3.0 ± 0.0	3.2 ± 0.4	3.0 ± 0.0	3.2 ± 0.4
	20	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.4 ± 0.5	3.4 ± 0.4
RT	5	38.9 ± 0.2	38.9 ± 0.1	38.8 ± 0.2	38.8 ± 0.2	38.8 ± 0.1	38.8 ± 0.2	38.8 ± 0.2	38.8 ± 0.1	38.7 ± 0.1
	10	38.7 ± 0.3	38.8 ± 0.2	38.8 ± 0.2	38.7 ± 0.2	38.8 ± 0.3	38.8 ± 0.2	38.8 ± 0.2	38.7 ± 0.3	38.7 ± 0.3
	20	38.9 ± 0.2	38.8 ± 0.2	38.8 ± 0.1	38.9 ± 0.1	38.8 ± 0.1	38.8 ± 0.2	38.8 ± 0.2	38.8 ± 0.2	38.8 ± 0.2

HR: heart rate, RR: respiratory rate, MAP: mean arterial pressure, RM: rumen motility, RT: rectal temperature. \*:  $p < 0.05$  versus 0 value

characteristics with lidocaine [6] and the sciatic nerve is consisted of the 6th lumbar, first and second sacral nerves, there will be also possibility of ataxia if more larger solution than 5 mL is administered as shown in this study. Also, solution injected into the epidural space distributes along the longitudinal epidural veins, which provide ideal conditions for rapid vascular absorption [13]. Sedation after epidural administration of xylazine is a typical sign of systemic absorption through the epidural veins in cattle [14,20,21]. Although epidural ketamine of high dose (about 2 mg/kg) caused only mild sedation in horses [8], cows of this study did not show sedation. This effect may be explained by the slow systemic absorption of ketamine from the epidural space [19]. This may come from species difference, such as the different caudal extent of the spinal cord within the different epidural space, and difference of administration method [8]. As a result of slow systemic absorption, there were no large changes in HR, RR, MAP and RM, which may reflect the concentration of ketamine in blood stream.

Production of caudal anesthesia depends upon the total dose (volume × concentration) of the anesthetic administered [22]. Recommended volume of solution for caudal epidural anesthesia is 5 to 10 mL in adult cattle or 1 mL per 100 kg of body weight [10,22]. In this study, the onset and area of analgesia after ketamine administration was rapid and similar with that of lidocaine [9], but the duration of analgesia was about a half of lidocaine [15]. However, if the similar volume (5-7 mL) was used with xylazine, an  $\alpha_2$ -adrenergic agonist, dermatomal analgesic area could broaden, and surgeries of flank, udder and scrotum could be performed in a standing position [4,5,25]. Although it has been considered that ketamine

acts on NMDA-receptors of the spinal cord, the spinal cord ends in the region of the last lumbar vertebra and the meningeal sac is continued as far as the junction of the 3rd and 4th sacral segments [10]. This difference is considered as effect of pharmacokinetic of ketamine, lidocaine and xylazine administered. Drugs that are either very hydrophilic (i.e., lidocaine) or very hydrophobic (i.e., medetomidine) have permeability coefficients that are significantly less than drugs of intermediate hydrophobicity (i.e., xylazine or clonidine) [2]. If ketamine has similar pharmacokinetic profile with lidocaine [6], analgesic effect after caudal epidural administration may be caused by similar mechanism with lidocaine. The reason for relative short duration of analgesia after epidural ketamine administration is not fully understood and more detail studies of neuropharmacology are needed.

In a point of clinical view, epidural administration of 20 mL ketamine is not suitable for standing surgery of tail and perineum because there is possibility of recumbency. The duration of analgesia after epidural administration of 5 and 10 mL ketamine is short for common surgical procedures and pain relief of perineum. However, it may be useful for obstetric procedures such as dystocia because there are minimal effects on cardiopulmonary and rumen functions. It seems likely that neither racemic nor S(+) ketamine will be clinically successful if used as sole therapy; only when used in combination with other drugs and treatments can secondary injury be effectively limited [11]. Further studies are needed to determine whether the analgesia is sufficient for surgery and whether the duration of analgesia can be prolonged by the concurrent use of other epidural drugs without systemic effects.

## References

1. **Beltrutti, D. P. C., Trompeo, A. C. and Santo, S. D.** The epidural and intrathecal administration of ketamine. *Curr. Rev. Pain* 1999, **3**, 458-472.
2. **Bernards, C. M. and Hill, H. F.** Physical and chemical properties of drug molecules governing their diffusion through the spinal meninges. *Anesthesiology* 1992, **77**, 750-756.
3. **Caron, J. P. and LeBlanc, P. H.** Caudal epidural analgesia in cattle using xylazine. *Can. J. Vet. Res.* 1989, **53**, 486-489.
4. **Caulkett, N., Cribb, P. H. and Duke, T.** Xylazine epidural analgesia for cesarean section in cattle. *Can. Vet. J.* 1993, **34**, 674-676.
5. **Caulkett, N. A., Cribb, P. H., MacDonald, D. G., Fretz, P. B. and Janzen, E. D.** Xylazine hydrochloride epidural analgesia: A method of providing sedation and analgesia to facilitate castration of mature bulls. *Comp. Contin. Educ. Pract. Vet.* 1993, **15**, 1155-1159.
6. **Dowdy, E. G., Kaya, K. and Gocho, Y.** Some pharmacologic similarities of ketamine, lidocaine, and procaine. *Anesth. Analg.* 1973, **52**, 839-842.
7. **Ferguson, J. D., Galligan, D. T. and Thomsen, N.** Principal descriptors of body condition score in Holstein cows. *J. Dairy Sci.* 1994, **77**, 2695-2703.
8. **Gomez De Segura, I. A., Rossi, R. D., Santos, M., San-Roman, J. L. and Tendillo, F. J.** Epidural injection of ketamine for perineal analgesia in the horse. *Vet. Anaesth. Analg.* 1998, **27**, 384-391.
9. **Grubb, T. L., Riebold, T. W., Crisman, R. O. and Lamb, L. D.** Comparison of lidocaine, xylazine, and lidocaine-xylazine for caudal epidural analgesia in cattle. *Vet. Anaesth. Analg.* 2002, **29**, 64-68.
10. **Hall, L. W., Clarke, K. W. and Trim, C. M.** *Veterinary Anaesthesia*. pp. 315-339. 10th ed. W. B. Saunders, London, 2001.
11. **Kohrs, R. and Durieux, M. E.** Ketamine: teaching on old drug new tricks. *Anesth. Analg.* 1998, **87**, 1186-1193.
12. **Lansdowne, J. L., Kerr, C. L., Boure, L. P. and Pearce, S. G.** Development and evaluation of epidural anesthesia for laparoscopy in foals (abstract). *Vet. Surg.* 2002, **31**, 487-488.
13. **Lee, I. H., Soehartono, R. H., Yamagishi, N., Taguchi, K. and Yamada, H.** Distribution of new methylene blue injected into the dorsolumbar epidural space in cows. *Vet. Anaesth. Analg.* 2001, **28**, 140-145.
14. **Lee, I., Yamagishi, N., Oboshi, K. and Yamada, H.** Effect of epidural fat on xylazine-induced dorsolumbar epidural analgesia in cattle. *Vet. J.* 2003, **165**, 330-332.
15. **Lin, H., Trachte, E. A., Degraives, F. J., Rodgerson, D. H., Steiss, J. E. and Carson, R. L.** Evaluation of analgesia induced by epidural administration of medetomidine to cows. *Am. J. Vet. Res.* 1998, **59**, 162-167.
16. **Martin, D. D., Tranquilli, W. J., Olson, W. A., Thurmon, J. C. and Benson, G. J.** Hemodynamic effects of epidural ketamine in isoflurane-anesthetized dogs. *Vet. Surg.* 1997, **26**, 505-509.
17. **Muir, W. W., Hubbell, J. A. E., Skarda, R. T. and Bednarski, R. M.** *Handbook of Veterinary Anesthesia*, pp. 57-81. 3rd ed. Mosby, St. Louis, 2000.
18. **Park, W. Y.** Factors influencing distribution of local anesthetics in the epidural space. *Reg. Anesth.* 1988, **13**, 49-57.
19. **Pedraz, J. L., Calvo, M. B., Gascon, A. R., Hernandez, R., Muriel, C., Torres, L. M. and Dominguez-Gil, A.** Pharmacokinetics and distribution of ketamine after extradural administration to dogs. *Br. J. Anaesth.* 1991, **67**, 310-316.
20. **Skarda, R. T., St. Jean, G. and Muir, W. W.** Influence of tolazoline on caudal epidural administration of xylazine in cattle. *Am. J. Vet. Res.* 1990, **51**, 556-560.
21. **St. Jean, G., Skarda, R. T., Muir, W. W. and Hoffsis, G. F.** Caudal epidural analgesia induced by xylazine administration in cows. *Am. J. Vet. Res.* 1990, **51**, 1232-1236.
22. **Thurmon, J. C., Tranquilli, W. J. and Benson, G. J.** *Lumb & Jones' Veterinary Anesthesia*, pp. 479-514. 3rd ed. Williams & Wilkins, Baltimore, 1996.
23. **Ting, S. T. L., Earley, B., Hughes, J. M. L. and Crowe, M. A.** Effect of ketoprofen, lidocaine local anesthesia, and combined xylazine and lidocaine caudal epidural anesthesia during castration of beef cattle on stress responses, immunity, growth, and behavior. *J. Anim. Sci.* 2003, **81**, 1281-1293.
24. **Wagner, A. E., Walton, J. A., Hellyer, P. W., Gaynor, J. S. and Mama, K. R.** Use of low doses of ketamine administered by constant rate infusion as an adjunct for postoperative analgesia in dogs. *J. Am. Vet. Med. Assoc.* 2002, **221**, 72-75.
25. **Zaugg, J. L. and Nussbaum, M.** Epidural injection of xylazine: A new option for surgical analgesia of the bovine abdomen and udder. *Vet. Med.* 1990, **85**, 1043-1046.