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The Antinociceptive Effects of Epidural Tramadol with Bupivacaine in Beagle Dogs

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Abstract : This study investigated the antinociceptive effect of epidural tramadol with bupivacaine in 36 healthy Beagle dogs. The dogs were divided into 6 groups; 1) C (control), 2) B (0.5% bupivacaine 0.1 mL/kg), 3) BT0.5 (0.5% bupivacaine 0.1 mL/kg + tramadol 0.5 mg/kg), 4) BT1 (0.5% bupivacaine 0.1 mL/kg + tramadol 1 mg/kg), 5) BT2 (0.5% bupivacaine 0.1 mL/kg + tramadol 2 mg/kg), 6) BT3 (0.5% bupivacaine 0.1 mL/kg + tramadol 3 mg/kg). The epidural injection was performed under isoflurane inhalation, after then, nociceptive block and motor block scores were assessed with physiologic parameters (HR, RR, RT, MAP). BT groups showed significantly longer antinociceptive time than C and B, while motor block time of BT groups were not different from B except BT3. Durations of total nociceptive block of BT2 (60.83 ± 19.08 min) and BT3 (74.17 ± 8.61 min) were significantly longer than those of BT0.5 (33.33 ± 8.76 min) and BT1 (37.50 ± 19.43 min), but there was no significant difference between BT2 and BT3. Durations of total motor block in all groups were less than 20 minutes although that of BT3 was significantly longer than B. There were no significant differences in HR, RR, RT, MAP among groups. Consequently, epidural administration of tramadol (2 mg/kg) with 0.5% bupivacaine (0.1 mL/kg) can be used safely and effectively in dogs.

Key words **:** epidural anesthesia, tramadol-bupivacaine, nociceptive block, motor block, dog.

Introduction

Pain in human medicine is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (4). But it is difficult to apply to animals, and as an alternative to that, an aversive sensory experience caused by actual or potential injury that elicits protective motor and vegetative reactions, results in learned avoidance and may modify species-specific behavior, including social behavior (38). In the past, it was considered that animals did not feel pain or that they did feel pain differently from humans. However, it is identified that pain pathways are similar in animals and humans (35).

Pain relief is often inadequate, and untreated pain has many undesirable consequences in animals (14,23). This contribute to biological, physiological and behavioral negative changes, which are in cortisol levels, protein catabolism, appetite, posture and cardiopulmonary function (16,17,21,22). These changes can result in depression of the immune response, delay in recovery, and even failure of the pulmonary, cardiovascular, or gastrointestinal systems. Therefore, a recognition, assessment, prevention, and treatment of pain are very important (3,22).

Pain relief is achieved by block of pain pathway. Administration of systemic analgesics is the most commonly used method of effective pain control. However, many analgesics administered by systemically have unwilling side effects sometimes, such as bradycardia following fentanyl constant rate infusion (31). An epidural anesthesia and analgesia (EAA) has shown to control the pain effectively, often without significant systemic effects. The EAA can be used to substitute or combine with other analgesic techniques (36). Also EAA may be administered as an adjunct to general anesthetic techniques, which results in reduction of the requirement of inhalant agents. Administration of EAA not only provides intra-operative analgesia or reduces a minimum alveolar concentration (MAC) of inhalant anesthetics, but also provides postoperative analgesia of prolonged duration (15,32). Historically, EAA was first experimentally performed in dogs in 1885 (8). Clinical usefulness of EAA was advocated in the 1950s (19,30). The studies of newer local anesthetics and opioids in the epidural space are reported in 1980s (12,34).

In dogs, a site of EAA is almost lumbo-sacral region. Because the epidural space is limited, the volume of drug can affect cranial migration of the drugs and epidural space pressure. Generally speaking, a volume of 1 mL per 5 kg of body weight blocks up to the first lumbar vertebra, and a maximum volume, 6 mL is accepted irrespective of patient size (18,33).

The most frequently used drug in dogs for EAA is lidocaine, which produces rapid onset and short duration of sensory and motor block. Bupivacaine is also used, however, it has slow onset but longer duration of action than lidocaine in dogs (18). Furthermore, epidural administration of bupivacaine shows longer duration of motor block in dogs (13). In human medicine, there was a rising interest on study of maintaining sensory block, but minimal motor block. Such methods include the continuous infusion of diluted drugs,

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addition of other drugs, and so on (37).

The epidural administration of an opioid with local anesthetics is one of the most common methods for pain control. The low dose opioids provide effective and long lasting analgesia via opioid receptors (28). Although epidural morphine, fentanyl, alfentanil and pethidine provide effective analgesia, repeated and continuous administration of epidural opioids did increase the adverse effects on respiratory depression, especially. Tramadol may be advantageous because of a low risk of respiratory depression (2,9). Tramadol is a μ-opioid agonist and a blocker of noradrenaline and serotonin reuptake (27). Various studies reported that tramadol produced a local and spinal anesthetic effect while also reducing the consumption of analgesics and prolong the postoperative analgesic period. Also it has little cardiovascular and respiratory depression (7,10,11). There was a study that no significant difference in the effectiveness of postoperative analgesia between morphine and tramadol given by the epidural route in female dogs submitted to ovariohysterectomy (25).

The mixture of bupivacaine and tramadol by epidural route are widely studied already in human medicine (6,20,26,29). However, there was no report about duration of analgesic effect or motor block of the epidural bupivacaine-tramadol mixture in dogs. The aim of this study is to investigate the antinociceptive effect and motor block effect of epidural tramadol with bupivacaine in dogs.

Materials and Methods

Animals

This study was approved by the Chungnam National University Animal Care and Use Committee. Thirty-six healthy male beagle dogs with body weight ranging from 6.5 to 11.5 kg (mean body weight: 8.91 kg, BCS 4-6/9) were included. The dogs were randomly assigned to 6 groups of 6 each; Control group (C); Bupivacaine group (B); Bupivacaine-Tramadol 0.5 group (BT0.5); Bupivacaine-Tramadol 1 group (BT1); Bupivacaine-Tramadol 2 group (BT2); Bupivacaine-Tramadol 3 group (BT3).

The dogs were assessed by means of physical examination and clinical laboratory analyses of complete blood count and serum biochemistry. All findings were within reference ranges. The dogs were fasted for 12 hours and water was withheld for 4 hours before the anesthesia.

Procedure

Before the procedure, baseline physiological parameters; heart rate (HR), respiratory rate (RR), rectal temperature (RT), blood pressure (BP) were measured. Intravenous fluid (0.9% sodium chloride solution, 60 mL/kg/day) was administered through the cephalic vein.

All dogs were pre-oxygenated for 5 minutes without premedication. The anesthesia was induced by mask inhalation of isoflurane (concentration was gradually increased up to 5%, Ifran liquid, Hana Pharm Co, Korea) under pure oxygen. After tracheal intubation, anesthetic status was maintained during epidural injection. All dogs were positioned in sternal recumbency. The pre-clipped epidural injection site was prepared aseptically. A 22-gauge spinal needle (Spinal needle, Taechang Industry, Co, Korea) was inserted into the lumbosacral epidural space. After confirmation of negative pressure using 1 ml syringe without aspiration of blood or cerebrospinal fluid (CSF), the selected drug-mixture within a same syringe was administered; 1) group C: 0.9% NaCl solution 0.22 mL/kg, 2) group B: 0.5% bupivacaine 0.1 mL/kg, 3) group BT0.5: 0.5% bupivacaine 0.1 mL/kg with tramadol 0.5 mg/kg, 4) group BT1: 0.5% bupivacaine 0.1 mL/kg with tramadol 1 mg/kg, 5) group BT2: 0.5% bupivacaine 0.1 mL/kg with tramadol 2 mg/kg, 6) group BT3: 0.5% bupivacaine 0.1 mL/kg with tramadol 3 mg/kg. Preservative-free bupivacaine (Bupivacaine HCl 0.5%, Myungmoon Pharm, Co, Korea) and tramadol (Toranzin® 100 mg/mL, Samsung Pharm, Co, Korea) were used and all experiments were proceeded in a blind manner. In all treatments, the drugs were diluted with a 0.9% NaCl solution to produce a total volume of 0.22 mL/kg. During the injection, 1 ml of free air in the syringe was not compressed. Isoflurane was discontinued at the point of completion of epidural injection and that time was recorded as 0-minute. The treated dog was maintained in sternal recumbency during the experiment. Pain response, walking status and physiological parameters were recorded.

Evaluation

Nociceptive block

The pain response was assessed by applying stimulus with an Allis tissue forcep clamped close to the first ratchet to the perineum and the toe-web with 5 minute intervals from epidural injection (0-minute) until normal response reoccurred. One same observer, unaware of which treatment had been given, assessed the response to the pain throughout all experiments. The pain response was graded as 3 score system; 1-no response, 2-reduced response, 3-normal response (withdrawal or vocalizing). Time to onset and duration of nociceptive block were recorded. The study times (in minute) were defined as following; 1) time to onset of nociceptive block: time from the epidural injection to the first reduction of the response (score < 3), 2) duration of complete nociceptive block: time during which complete analgesia was observed (score $= 1$), 3) duration of total nociceptive block: time during which analgesia, whether partial or complete, was observed (score < 3).

Motor block

The motor function was assessed by standing time and walking status at 5 minute intervals from epidural injection (0-minute) until normal walking observed. The walking status was graded as 4 score system; 1-unable to walk, 2-marked stumbling, very ataxic, 3-slight stumbling, 4-normal walking. The duration of motor block was also recorded. The study times (in minute) were defined as following; 1) duration of complete motor block: time from the epidural injection to the first standing (score=1), 2) duration of total motor block: time from the epidural injection to the normal walking (score < 4).

Physiological variables

The HR, RR, RT and MAP were measured before (baseline), immediately after the epidural injection (0-minute), at

10 minute intervals for 60 minutes, and then at 60 minute intervals thereafter until the end the study. HR in beats/minute was measured by auscultation with a stethoscope. RR was counted the numbers of breath/minute by observation and RT was measured by using a digital clinical thermometer in degrees Celsius (°C). MAP was measured by noninvasive method using oscillometric blood pressure monitor (Cardell® 9402, Sharm Vet Inc, USA).

Statistical analysis

Data were expressed as a mean ± standard deviation (SD). Statistical analysis was performed using IBM SPSS Statics 21.0 (SPSS Inc, USA).

To assess the difference of sensory and motor blocked duration among the groups, one-way analysis of variance (ANOVA) was used with post hoc analysis by Duncan when a significant difference was noticed. Difference in sensory block between right and left limb was not evaluated. Physiological variables were compared using repeated ANOVA followed by Dunnett-t and Tukey.

For all analyses, a value of $p < 0.05$ was considered as statistically significant.

Results

Nociceptive block

The onset of nociceptive block was similar among all groups and mean onset time was within 5 to 7 minutes. Both durations of complete nociceptive block and total nociceptive block were significantly longer in tramadol mixture groups than control and bupivacaine alone group. There was no significant difference between group B and C. As the doses of tramadol were increased, the durations of complete nociceptive block and total nociceptive block were prolonged. But, group BT0.5 and group BT1 were not significantly different. Also, group BT2 and group BT3 were not significantly different (Table 1).

Motor block

There were no significant differences of duration of complete motor block among all groups. The duration of total motor block was significantly longer in group BT3 than group C, group B, and group BT0.5. There were no significant differences in duration of total motor block among group BT1, group BT2 and group BT3 (Table 2).

Physiological variables

There were no significant differences in HR, RR, RT and MAP among groups. In HR, significant difference from the baseline was shown at 10 minutes in group BT1 and group BT3, and at 20 minutes in group BT3 (Table 3). RR did not differ from base-line with any treatment or time points within same group (Table 4). In RT, significant differences from the baseline were observed at 0 minutes and 10 minutes in all groups except group BT2, and at 20 minutes in group BT1 and group BT3 (Table 5). In MAP, significant difference from the baseline was shown only at 20 minutes in group C (Table 6).

Table 1. Onset and duration of nociceptive block of epidural tramadol-bupivacaine in Beagle dogs

Group	Onset of block	Duration of complete block	Duration of total block
C	5.00 ± 0.00	0.83 ± 2.04[a]	1.67 ± 2.58[a]
B	6.67 ± 4.08	5.00 ± 4.47[b]	11.67 ± 6.06[b]
BT0.5	5.83 ± 2.04	20.83 ± 8.61[abc]	33.33 ± 8.76[abc]
BT1	5.83 ± 2.04	18.33 ± 15.06[abd]	37.50 ± 19.43[abd]
BT2	5.00 ± 0.00	35.00 ± 12.65[abcd]	60.83 ± 19.08[abcd]
BT3	5.00 ± 0.00	36.33 ± 12.91[abcd]	74.17 ± 8.61[abcd]

Data are expressed in minute as mean ± SD of each group (n = 6). C: control, B: 0.5% bupivacaine 0.1 mL/kg, BT0.5: 0.5% bupivacaine 0.1 mL/kg with tramadol 0.5 mg/kg, BT1: 0.5% bupivacaine 0.1 mL/kg with tramadol 1 mg/kg, BT2: 0.5% bupivacaine 0.1 mL/kg with tramadol 2 mg/kg, BT3: 0.5% bupivacaine 0.1 mL/kg with tramadol 3 mg/kg

[a,b,c,d]Groups sharing the same superscript letter differ significantly from each other ($p < 0.05$).

Table 2. Duration of motor block of epidural tramadol-bupivacaine in Beagle dogs

Group	Duration of complete block	Duration of total block
C	4.33 ± 0.52	10.83 ± 2.04[a]
B	6.83 ± 2.79	14.17 ± 3.76[b]
BT0.5	6.00 ± 2.19	14.17 ± 3.76[c]
BT1	7.00 ± 1.55	15.00 ± 3.16[a]
BT2	6.33 ± 1.97	16.67 ± 2.58[a]
BT3	7.50 ± 4.09	18.33 ± 2.58[abc]

Data are expressed in minute as mean ± SD of each group (n = 6). C: control, B: 0.5% bupivacaine 0.1 mL/kg, BT0.5: 0.5% bupivacaine 0.1 mL/kg with tramadol 0.5 mg/kg, BT1: 0.5% bupivacaine 0.1 mL/kg with tramadol 1 mg/kg, BT2: 0.5% bupivacaine 0.1 mL/kg with tramadol 2 mg/kg, BT3: 0.5% bupivacaine 0.1 mL/kg with tramadol 3 mg/kg

[a,b,c]Groups sharing the same superscript letter differ significantly from each other ($p < 0.05$).

Discussion

In human medicine, administration of epidural tramadol with bupivacaine has been used successfully, providing prolonged analgesic effect without severe adverse effect (6,20, 26,29). However, there was little information of epidural tramadol with bupivacaine in dogs. Bunnag and Durongphongtorn examined the analgesic efficacy of EAA of 0.5% bupivacaine 0.16 mL/kg, 0.5% bupivacaine 0.16 mL/kg mixed with morphine 0.1 mg/kg, or 0.5% bupivacaine 0.16 mL/kg mixed with tramadol 2 mg/kg in dogs undergoing stifle surgery and reported that dogs in all treatment groups required level of isoflurane to less than 1 MAC throughout the surgical manipulation. However, there was no information about duration of analgesic effects (5).

This study investigated the duration of nociceptive block and motor block of epidural tramadol with bupivacaine in dogs. The doses of bupivacaine and tramadol for EAA in

Table 3. Heart rate (HR) in beagle dogs following the epidural administration of tramadol-bupivacaine

Group	pre	0	10	20	30	40	50	60	120	180	240
C	103.50 ± 8.53	108.50 ± 34.44	120.17 ± 32.72	107.33 ± 26.81	94.33 ± 12.18	93.33 ± 5.65	97.67 ± 5.13	96.83 ± 7.83	100.17 ± 11.79	91.33 ± 15.57	91.83 ± 20.85
B	97.17 ± 9.90	101.83 ± 16.49	106.00 ± 19.59	102.67 ± 26.11	95.50 ± 15.18	98.50 ± 12.53	94.50 ± 17.56	99.00 ± 10.30	98.17 ± 12.50	89.83 ± 11.11	91.83 ± 12.01
BT0.5	100.50 ± 20.61	104.17 ± 3.13	108.50 ± 33.79	100.83 ± 19.19	101.33 ± 20.05	101.83 ± 20.84	97.17 ± 15.92	90.83 ± 18.84	94.67 ± 15.57	95.17 ± 17.96	87.67 ± 12.23
BT1	98.50 ± 11.08	102.67 ± 11.79	122.50 ± 17.50*	114.33 ± 7.31	109.50 ± 13.64	107.83 ± 9.22	105.17 ± 12.16	104.50 ± 14.32	99.17 ± 10.46	96.33 ± 14.01	92.17 ± 8.50
BT2	115.17 ± 20.59	114.83 ± 25.80	123.50 ± 12.49	114.67 ± 19.65	115.0 ± 11.83	114.17 ± 16.88	110.50 ± 14.46	105.83 ± 13.54	105.33 ± 13.47	98.00 ± 12.60	104.33 ± 9.09
BT3	89.00 ± 13.12	101.17 ± 19.15	110.50 ± 5.21*	112.17 ± 16.64*	96.33 ± 12.57	96.33 ± 12.97	100.17 ± 13.93	86.83 ± 15.34	82.83 ± 6.21	83.33 ± 10.56	85.83 ± 7.28

Data are expressed in beats per minute as mean ± SD of each group (n = 6).
C: control, B: 0.5% bupivacaine 0.1 mL/kg, BT0.5: 0.5% bupivacaine 0.1 mL/kg with tramadol 0.5 mg/kg, BT1: 0.5% bupivacaine 0.1 mL/kg with tramadol 1 mg/kg, BT2: 0.5% bupivacaine 0.1 mL/kg with tramadol 2 mg/kg, BT3: 0.5% bupivacaine 0.1 mL/kg with tramadol 3 mg/kg
*Significantly different from the baseline ($p < 0.05$).

Table 4. Respiratory rate (RR) in beagle dogs following the epidural administration of tramadol-bupivacaine

Group	pre	0	10	20	30	40	50	60	120	180	240
C	21.00 ± 6.42	19.33 ± 10.62	24.00 ± 3.58	24.67 ± 6.28	23.67 ± 4.80	22.83 ± 3.13	21.17 ± 5.88	24.00 ± 3.58	21.67 ± 4.46	20.67 ± 4.68	21.33 ± 4.84
B	19.67 ± 3.93	23.33 ± 10.00	21.33 ± 3.88	20.00 ± 2.28	19.67 ± 2.94	18.33 ± 1.86	19.83 ± 4.49	19.50 ± 3.08	20.83 ± 3.00	23.17 ± 2.72	23.33 ± 5.50
BT0.5	23.67 ± 4.80	23.50 ± 11.49	20.67 ± 4.68	23.83 ± 7.81	22.33 ± 9.67	23.33 ± 5.50	22.00 ± 5.66	22.17 ± 5.31	22.67 ± 7.45	24.17 ± 5.08	23.33 ± 3.93
BT1	24.50 ± 6.12	23.33 ± 9.63	21.50 ± 3.56	23.83 ± 2.40	22.17 ± 2.04	23.67 ± 4.59	22.00 ± 5.66	20.83 ± 4.67	22.17 ± 4.12	21.33. ± 4.84	21.33 ± 5.28
BT2	24.83 ± 5.31	17.50 ± 5.43	26.50 ± 6.50	28.50 ± 3.89	26.50 ± 5.13	28.33 ± 8.24	28.83 ± 4.12	26.00 ± 4.20	23.83 ± 4.92	23.50 ± 5.43	26.83 ± 2.23
BT3	23.33 ± 4.68	18.00 ± 4.20	19.00 ± 3.03	21.50 ± 4.09	22.00 ± 2.19	22.33 ± 4.08	20.67 ± 3.01	20.67 ± 3.01	20.83 ± 3.00	20.83 ± 3.00	20.17 ± 2.23

Data are expressed breaths pre minute as mean ± SD of each group (n = 6).
C: control, B: 0.5% bupivacaine 0.1 mL/kg, BT0.5: 0.5% bupivacaine 0.1 mL/kg with tramadol 0.5 mg/kg, BT1: 0.5% bupivacaine 0.1 mL/kg with tramadol 1 mg/kg, BT2: 0.5% bupivacaine 0.1 mL/kg with tramadol 2 mg/kg, BT3: 0.5% bupivacaine 0.1 mL/kg with tramadol 3 mg/kg

Table 5. Rectal temperature (RT) in beagle dogs following the epidural administration of tramadol-bupivacaine

Group	pre	0	10	20	30	40	50	60	120	180	240
C	38.40 ± 0.56	37.63 ± 0.34*	37.82 ± 0.43*	38.12 ± 0.32	38.20 ± 0.15	38.27 ± 0.21	38.25 ± 0.26	38.20 ± 0.35	37.98 ± 0.40	37.95 ± 0.28	38.05 ± 0.36
B	38.47 ± 0.23	37.77 ± 0.39*	37.53 ± 0.64*	38.02 ± 0.52	38.08 ± 0.48	38.27 ± 0.37	38.37 ± 0.31	38.30 ± 0.18	38.20 ± 0.24	38.13 ± 0.23	38.15 ± 0.24
BT0.5	38.42 ± 0.72	37.60 ± 0.44*	37.68 ± 0.67*	38.07 ± 0.36	38.28 ± 0.24	38.38 ± 0.27	38.48 ± 0.26	38.48 ± 0.25	38.35 ± 0.31	38.23 ± 0.20	38.28 ± 0.16
BT1	38.47 ± 0.29	37.57. ± 0.36*	37.53 ± 0.23*	37.80 ± 0.20*	38.02 ± 0.22	38.08 ± 0.31	38.30 ± 0.44	38.43 ± 0.26	38.05 ± 0.29	38.08 ± 0.13	38.12 ± 0.20
BT2	38.38 ± 0.49	38.10 ± 0.33	38.10 ± 0.37	38.27 ± 0.37	38.58 ± 0.13	38.70 ± 0.34	38.77 ± 0.33	38.73 ± 0.26	38.27 ± 0.31	38.22 ± 0.25	38.28 ± 0.23
BT3	38.55 ± 0.41	37.23 ± 0.39*	37.37 ± 0.41*	37.72 ± 0.41*	38.08 ± 0.29	38.18 ± 0.26	38.28 ± 0.19	38.48 ± 0.13	38.18 ± 0.13	38.10 ± 0.24	38.32 ± 0.15

Data are expressed in degrees Celsius as mean ± SD of each group (n = 6).
C: control, B: 0.5% bupivacaine 0.1 mL/kg, BT0.5: 0.5% bupivacaine 0.1 mL/kg with tramadol 0.5 mg/kg, BT1: 0.5% bupivacaine 0.1 mL/kg with tramadol 1 mg/kg, BT2: 0.5% bupivacaine 0.1 mL/kg with tramadol 2 mg/kg, BT3: 0.5% bupivacaine 0.1 mL/kg with tramadol 3 mg/kg
*Significantly different from the baseline ($p < 0.05$).

Table 6. Mean blood pressure (MAP) in beagle dogs following the epidural administration of tramadol-bupivacaine

Group	pre	0	10	20	30	40	50	60	120	180	240
C	118.67 ± 4.41	98.33 ± 21.75	98.00 ± 16.78	95.33 ± 17.24*	100.00 ± 6.00	102.67 ± 12.66	103.17 ± 10.13	100.83 ± 13.38	112.67 ± 14.73	104.50 ± 10.25	106.83 ± 9.75
B	114.17 ± 15.97	99.33 ± 12.47	118.33 ± 5.61	104.17 ± 8.89	114.33 ± 14.29	112.83 ± 10.11	117.67 ± 13.82	108.67 ± 13.19	109.50 ± 6.32	109.67 ± 13.50	108.33 ± 8.71
BT0.5	98.83 ± 10.52	100.67 ± 19.16	109.67 ± 15.76	111.17 ± 10.27	117.00 ± 17.10	98.00 ± 16.88	103.83 ± 16.80	104.67 ± 13.82	86.83 ± 7.83	115.83 ± 10.59	94.67 ± 16.87
BT1	107.50 ± 13.02	100.00 ± 20.42	102.33 ± 17.36	110.33 ± 8.57	106.50 ± 18.36	106.33 ± 10.25	106.00 ± 5.40	106.83 ± 13.60	98.00 ± 14.91	109.00 ± 6.72	110.50 ± 13.11
BT2	102.17 ± 21.12	93.50 ± 18.33	100.67 ± 10.80	103.67 ± 16.00	111.00 ± 7.51	106.33 ± 14.60	100.33 ± 15.37	103.00 ± 14.13	108.50 ± 11.43	100.83 ± 13.06	104.33 ± 14.98
BT3	100.00 ± 15.00	88.50 ± 20.72	105.33 ± 18.90	101.50 ± 15.06	101.33 ± 15.85	96.50 ± 9.46	98.83 ± 11.81	93.00 ± 10.28	103.00 ± 6.26	95.00 ± 11.61	102.17 ± 12.70

Data are expressed in mmHg as mean ± SD of each group (n = 6).
C: control, B: 0.5% bupivacaine 0.1 mL/kg, BT0.5: 0.5% bupivacaine 0.1 mL/kg with tramadol 0.5 mg/kg, BT1: 0.5% bupivacaine 0.1 mL/kg with tramadol 1 mg/kg, BT2: 0.5% bupivacaine 0.1 mL/kg with tramadol 2 mg/kg, BT3: 0.5% bupivacaine 0.1 mL/kg with tramadol 3 mg/kg
*Significantly different from the baseline ($p < 0.05$).

dogs for the present study were set to produce maximum nociceptive block and minimum motor block.

The results showed that the onset time of the nociceptive block was not significantly different among all groups. But the durations of complete nociceptive block and total nociceptive block were significantly longer in tramadol-bupivacaine mixture groups than control and bupivacaine alone groups. There were no significant differences between group C and group B. When bupivacaine is used epidurally alone, the indicated dose is 1.0-2.2 mg/kg which is 2-4.4 folds to that of this study (36). Previous human studies reported that the epidural tramadol with bupivacaine provides prolonged and good postoperative analgesic quality compared to plain bupivacaine (6,20,26,29).

Prakash reported that epidural administrations of bupivacaine with different doses of tramadol showed a dose-related increase in analgesic effect in children underwent inguinal herniotomy (26). In current study, durations of total nociceptive block were 33.33 ± 8.76 minutes (group BT0.5), 37.50 ± 19.43 minutes (group BT1), 60.83 ± 19.08 minutes (group BT2), and 74.17 ± 8.61 minutes (group BT3), respectively; BT2 and BT3 showed significantly longer block than BT0.5 and BT1. The epidural administration of 1 mg/kg or less of tramadol with bupivacaine did not produce satisfactory durations of nociceptive block. The epidural administration of 2 mg/kg or more of tramadol with bupivacaine did produce satisfactory durations of nociceptive block. However, it seemed like that there was no need to administer 3 mg/kg or more of tramadol with bupivacaine in EAA in dogs; durations of nociceptive block of BT3 were not significantly different from those of BT2. Durations of analgesia of previous studies were much longer than that of this study. Natalini and colleagues reported that epidural administration of tramadol 1.0 mg/kg in 0.22 mL/kg of sterile water provided satisfactory antinociception and analgesia for 5.5 hours in dogs undergoing stifle surgery (24). Almeida and colleagues reported that epidurally administered 2% lidocaine 6.0 mg/kg combined tramadol 1.0 mg/kg provided analgesic effect for 24 hours and significantly longer duration of analgesia for 12 hours when compared to lidocaine 6.0 mg/kg combined morphine 0.1 mg/kg in dogs undergoing orchiectomy (1). This might be caused by different assessment methods, thus, clamping score versus physiologic and behavioral (activity and posture) score.

Durations of complete motor block were not significantly different among all groups. The longest duration of total motor block was 18.33 ± 2.58 minutes in BT3 which was significantly different from group C, group B and group BT0.5. However, there were no significant differences among group BT1, group BT2 and group BT3. All dogs showed normal walking within 20 minutes. These results were inconsistent with previous study reported that 0.5% bupivacaine 0.25 mL/kg provided motor block up to 158.3 minutes in dogs (13). But, the dose of 0.1 mL/kg of 0.5% bupivacaine was used in present study, which might result in minimal motor block effects. Prakash and colleagues reported that epidurally administered 0.25% bupivacaine 0.75 mL/kg, 0.25% bupivacaine 0.75 mL/kg with tramadol 1.0 mg/kg, or 0.25% bupivacaine 0.75 mL/kg with tramadol 1.5 mg/kg, or 0.25% bupivacaine 0.75 mL/kg with tramadol 2.0 mg/kg showed no motor block in children underwent inguinal herniotomy (26). This might be not comparable because the different dose of bupivacaine as well as difference in maintenance of the general anesthesia. In their study, general anesthesia was maintained about 35 minutes after epidural injection, but isoflurane was discontinued at the completion of epidural injection in this study.

In this study, all treatments produce minimal physiological changes in the HR, RR, RT, MAP within and among the groups. RT decreased relatively to the baseline at the early part of experiment and it was considered that normal changes after administration of isoflurane.

As for all this study's results, group BT0.5 and group BT1 showed relatively short durations of total nociceptive block, while that of group BT2 and group BT3 were significantly longer. But, there was no significant difference between group BT2 and group BT3. Duration of total motor block in group BT3 was longest (18.33 ± 2.58 minutes) although it was not significantly different from group BT2. The minimal changes in physiological parameters can be interpreted as minimal systemic side effects.

Epidural administration of tramadol with bupivacaine provided favorable antinociception than bupivacaine alone, with minimal motor block and rapid onset. Epidural administration of tramadol (2 mg/kg) with bupivacaine (0.5%, 0.1 mL/kg) can be used safely and effectively for EAA in dogs. Although one-hour block could be relatively short, it can be useful in minor procedure, or expected to provide a MAC sparing effect in adjuvant to general anesthesia. Further study is needed to evaluate intra-operative usefulness of and post-operative analgesic property of bupivacaine combined tramadol EAA method in dogs. Another repetitive study with increased bupivacaine volume also might be considered to assess whether total antinociceptive duration is elongated.

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