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**Evaluation of Factors Influencing  
Epidural Anesthesia in Dogs**

개의 경막외마취에 영향을 미치는 인자의 평가

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# **Evaluation of Factors Influencing Epidural Anesthesia in Dogs**

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# **Evaluation of Factors Influencing Epidural Anesthesia in Dogs**

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## **ABSTRACT**

This study was performed to establish practical guidelines for epidural anesthesia (EA) through evaluation of factors influencing EA in dogs, and consists of four chapters.

In chapter I, the effect of ‘difference in vertebral height at the thoracolumbar region’ on EA was verified using the needle technique in sternally recumbent dogs. Contrast medium-methylene blue (CM-MB) mixture was injected at the lumbosacral (L7-S1) epidural space for evaluation of cranial spread according to the perpendicular height (PH) and angle of the upward slope (from the injection point to the highest vertebra) along the epidural canal. However, the epidural spread did not show significant correlations with PH and angle. The CM-MB mixture facilitated

the hydrodynamic study of epidural solution, and it was verified that the upward slope had no significant inhibitory effect on the cranial spread of epidural solution.

In chapter II, the effect of ‘epidural pressure according to injection speed’ on EA was verified using the needle technique. Two spinal needles connected to electrical pressure transducers were inserted into the L6-L7 and the L7-S1 epidural spaces to measure epidural and injection pressure (EP and IP, respectively) during injection of a bupivacaine-iohexol mixture via the spinal needle at L7-S1. After injection with two speeds (1 and 2 ml/minute), epidural distribution (ED) and sensory blockade (SB) were evaluated. Significant differences were observed according to injection speed for peak EP and peak IP, but not for ED and SB. Separating the epidural injection and pressure monitoring lines facilitated accurate EP profiling during injection, and it was verified that the increase in epidural injection speed increased the EP, but not the epidural spread or blockade.

In chapter III, the ‘volume effect of local anesthetic solution’ on thoracic EA was evaluated using the catheter technique. Epidural injection of lidocaine with four different volumes (0.05, 0.10, 0.15, and 0.20 ml/kg) was performed at the seventh thoracic epidural space via an epidural catheter. The extent and homogeneity of dermatomal SB increased according to the volumes administered. Some dogs showed temporary neurologic signs (Horner’s syndrome, paraplegia, ataxia, depression, and stupor) which had a tendency to increase in their frequency and severity when high volumes were administered. The results suggested that not only the extent of epidural blockade, but also its homogeneity and neurologic complications, should be concurrently considered when choosing an injectate volume of local anesthetics.

In chapter IV, the clinical application of thoracic EA with a catheter was evaluated in dogs. Bupivacaine or a bupivacaine-morphine combination was repeatedly administered at 0.2 ml/kg to provide intra- and postoperative analgesia after amputation of the right thoracic limb (n = 2) and thoracotomy for pulmonary lobectomy (n = 1). Effective analgesia was shown with minimal systemic effects. However, sudden paraplegia was observed in the thoracotomy case, and acute intervertebral disc disease was diagnosed through magnetic resonance imaging. These results suggested that clinical application of EA requires a coordinated multidisciplinary approach for safe and effective pain management without complications.

Through the present studies, it was verified that EA was primarily influenced by injection volume, but not by the difference in vertebral height in sternal recumbency or epidural pressure according to injection speed. In addition, higher injection volume increased not only the extent of SB and ED, but also their homogeneity. Therefore, a relatively high volume of injectate is recommended to provide even and adequate analgesia when performing EA using an epidural catheter as well as a needle. However, the use of EA requires a coordinated multidisciplinary approach to reduce the occurrence of potential complications.

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**Keywords: epidural anesthesia, influencing factor, injection volume, epidural needle, epidural catheter, dog**

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## LIST OF ABBREVIATIONS

<b>ANOVA</b>	Analysis of variance
<b>ASA</b>	American Society of Anesthesiologists
<b>BCS</b>	Body condition score
<b>C</b>	Cervical vertebra
<b>CE</b>	Cauda equina
<b>CM</b>	Contrast medium
<b>CNS</b>	Central nervous system
<b>CRI</b>	Constant rate infusion
<b>CSF</b>	Cerebrospinal fluid
<b>CT</b>	Computed tomography
<b>DM</b>	Dura mater
<b>EA</b>	Epidural anesthesia
<b>ECG</b>	Electrocardiogram
<b>ED</b>	Epidural distribution
<b>EP</b>	Epidural pressure
<b>f<sub>R</sub></b>	Respiratory rate
<b>G</b>	Gauge
<b>IP</b>	Injection pressure
<b>IV</b>	Intravenous
<b>IVDD</b>	Intervertebral disc disease

## **LIST OF ABBREVIATIONS (cont'd)**

<b>L</b>	Lumbar vertebra
<b>L7-S1</b>	Lumbosacral intervertebral space
<b>LF</b>	Ligamentum flavum
<b>MB</b>	Methylene blue
<b>NRF</b>	No remarkable findings
<b>OP</b>	Operation
<b>P<sub>E</sub>´CO<sub>2</sub></b>	End-tidal carbon dioxide tension
<b>PH</b>	Perpendicular height
<b>sAP</b>	Arterial blood pressure
<b>SB</b>	Sensory blockade
<b>SC</b>	Spinal cord
<b>SpO<sub>2</sub></b>	Hemoglobin oxygen saturation
<b>T</b>	Thoracic vertebra
<b>TEA</b>	Thoracic epidural analgesia
<b>V</b>	Volume treatment

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# GENERAL INTRODUCTION

Epidural anesthesia (EA) has a history of over a century in small animals, with the first documented use in experimental dogs in 1885 (Corning, 1885). Its clinical use began from the mid-twentieth century, when veterinary anesthesiologists routinely administered single epidural injection of local analgesics via an epidural needle for intraoperative analgesia before the appearance of an indwelling epidural catheter (Hansen, 2001). In the late twentieth century, the clinical use of an epidural catheter in small animals was attempted as an analgesic technique for patients in the intensive care unit, and its use facilitated continuous delivery of analgesic solution to the spinal neuraxis (Wetmore and Glowaski, 2000; Hansen, 2001). Consequently, EA has widened its field of use from intraoperative analgesia to prolonged analgesia after surgery or during critical care.

Epidural blockade has many advantages over other analgesic protocols that do not include regional techniques (Freise and Van Aken, 2011), but they are noted only when the blockade area is adequately generated. There have been many reports regarding inadequate analgesia followed by incomplete epidural distribution, which is characterized by insufficient range along the epidural canal, unilateral blockade, and/or complete deviation from the target segment (Hogan, 1999; Hansen, 2001; Yokoyama et al., 2004). These unexpected results have motivated further research to evaluate the influencing factors on epidural blockade. In humans, the influence of drug factors (volume, dose, concentration, and additives), patient factors (age, pregnancy, weight, height, and pressure in adjacent body cavities), and procedure factors (level of injection, patient position, speed of injection, and needle orifice

direction) on EA have been verified and classified, according to their significance, as major, minor, or none (Visser et al., 2008). However, since animals cannot verbally describe their pain, animal studies on pain assessment related to EA have limitations and are insufficient compared to those of humans. In small animals, studies have examined the effects of several major factors (drug volume, dose of specific drugs, etc.) on the spread of epidural analgesia in dogs (Feldman et al., 1996; Hendrix et al., 1996; Gomez de Segura et al., 2000; Freire et al., 2010), but further studies are required to verify the effects of difference in vertebral height at the thoracolumbar junction in sternal recumbency, and epidural pressure according to injection speed. In addition, considering recent use of the epidural catheter technique, not only are studies regarding major influencing factors (e.g. drug volume) lacking, but evaluation of its use in clinical cases were also required in dogs.

Therefore, this study was performed to verify the influencing factors on EA in dogs. The factors were included 1) difference in vertebral height at the thoracolumbar junction in sternal recumbency (Chapter I), 2) epidural pressure according to injection speed (Chapter II), and 3) volume of epidural solution in thoracic EA using a catheter technique (Chapter III). In addition, 4) clinical use of EA using the catheter technique was evaluated for adequate analgesia in dogs (Chapter IV).

# CHAPTER I.

## **Cranial Epidural Spread of Contrast Medium and Methylene Blue Dye in Sternally Recumbent Anesthetized Dogs**

### **Abstract**

This study was performed to examine the spread of solution injected at the lumbosacral (L7-S1) epidural space of sternally recumbent dogs.

Ten healthy adult Beagle dogs were anesthetized with total intravenous (IV) propofol infusion, and placed in sternal recumbency. A volume of 0.2 ml/kg contrast medium (CM) containing 1% new methylene blue (MB) dye was administered into the L7-S1 epidural space. Left to right lateral radiographs using a horizontal beam were taken every 5 minutes for 45 minutes. The perpendicular height (PH) between floor of the epidural canal of the highest vertebra and that of lumbosacral spinal canal was measured on radiographs. The angle of slope from the injection point toward the highest vertebral floor was measured. Immediately after taking the last radiographic image, dogs were euthanized and a laminectomy was performed from the cervical to lumbar vertebrae for visual evaluation of MB spread. The spread of CM and of MB as counted in number of stained vertebra were compared, and each of these data sets was further compared to PH and angle, using linear regression analyses.

The mean  $\pm$  SD of PH and angle were  $3.8 \pm 0.8$  cm and  $14.8 \pm 2.8^\circ$ , respectively. The peak cranial spread of CM was at  $12.7 \pm 5.7$  (range: C7-L3) vertebrae, and at

14.0 ± 5.4 (range: C6-L2) vertebrae for MB staining. There were no significant correlations between PH and spread of CM ( $R^2 = 0.08$ ) or MB ( $R^2 = 0.13$ ), between angle and spread of CM ( $R^2 = 0.05$ ) or MB ( $R^2 = 0.02$ ), respectively. CM and MB demonstrated a proportional relationship ( $R^2 = 0.82$ ,  $p < 0.001$ ).

It is noted that no significant inhibitory effect of upward slope on cranial epidural spread of the solution was observed. Other factors may have greater effect on epidural spread in sternally recumbent dogs.

## **Introduction**

Epidural administration of analgesic agents at the L7-S1 in dogs is a popular anesthetic technique for surgery such as tail amputation, perianal surgery or cesarean section. It is also used to provide adequate analgesia for labour and for postoperative pelvic limb pain (Jones, 2001; Skarda and Tranquilli, 2007). However, although the procedure is performed by the same clinician utilizing an identical technique, in some cases the target spinal segments are not reached, and analgesia is inadequate.

In humans, factors including injection volume, rate of infusion, patency of intervertebral foramina, posture, gravity, baricity, and vascular absorption have been reported to influence the outcome of the epidural analgesia (Bromage, 1962; 1975). In animals, such factors have been classified into physical characteristics of the animal, technical factors, intrinsic anatomic factors and epidural pressure (Lee et al., 2001; 2002; 2004). Studies have examined the effects of some of these technical factors, such as volume and concentration of specific drugs, on epidural analgesia spread in dogs (Feldman et al., 1996; Hendrix et al., 1996; Gomez de Segura et al., 2000; Freire et al., 2010), but further studies are required to understand how and for how long the spread of analgesics occur in the epidural space following injection of solution.

Positioning of the patient during and following epidural injection has been suggested as a significant factor on the outcome of epidural analgesia. If a unilateral coverage of analgesia is required, it is generally accepted that the desired area is placed as the dependent side, and for bilateral effect the patient placed in dorsal recumbency (Jones, 2001). This practice is based on the surmise that the gravity within the epidural cavity (which is sized from 1 to 2 cm in dogs) may play a significant role in the spread of analgesics. In dogs placed in sternal recumbency, in

a 'natural' position with their hind-limbs flexed, an upward slope of the epidural canal is created by a difference in PH between the lowest seventh lumbar vertebrae (L7) to the highest twelfth or thirteenth thoracic vertebra (T12 or T13) (Fig. 1). If gravity has an effect on the epidural space, it may be that the upward slope of the epidural canal from the injection point at the L7-S1, inhibits the cranial spread of injected solution from the L7-S1.

This study was performed to evaluate the spread of solution injected within the L7-S1 epidural space of sternally recumbent dogs, and to examine if cranial spread appeared to be influenced by the PH induced by the position of the dogs.

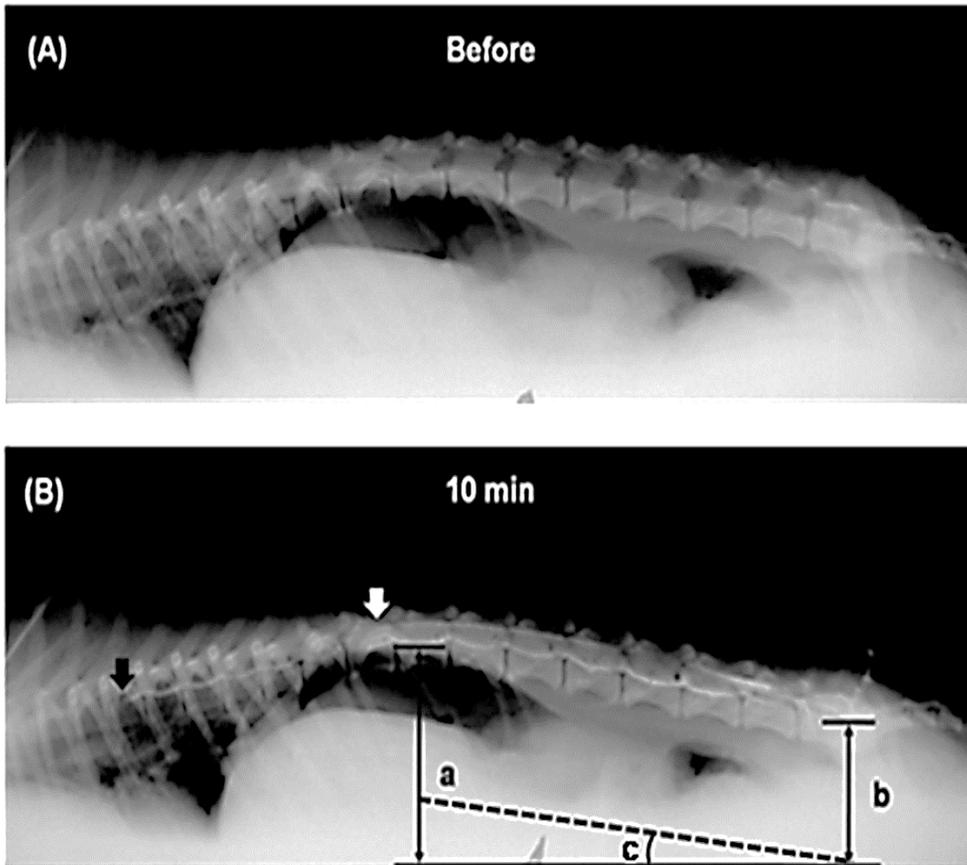


Fig. 1. Left to right lateral radiographs taken with horizontal beam before (A) and 10 minute after epidural injection (B) of contrast media in a sternally recumbent dog. These show the cranial spread of the contrast medium in the ventral (black arrow) and dorsal (white arrow) aspect of the spinal canal. The perpendicular height (PH) between ventral epidural surface of 13th thoracic (a) and lumbosacral epidural space (b) was also calculated on radiograph and revised with magnification factor (0.89). PH is (a) minus (b), and (c) is angle of upward epidural slope from injection point.

## **Materials and Methods**

### **1. Animals**

All experimental procedures were approved by the Ethics Committee of the Seoul National University (SNU-080805-4). The subjects were clinically healthy Beagles (8 males and 2 females) that were part of an orthopedic research project and were scheduled for euthanasia for histological analysis as part of that study. The orthopedic research was limited to the thoracic limbs, and therefore the current study would not interfere with those results. Body condition score (BCS) of the dogs was assessed based on previously described methods (Lund et al., 1999). Dogs were  $4.0 \pm 0.9$  (mean  $\pm$  SD) years old, body weight  $7.6 \pm 1.1$  kg and median (ranges) of BCS was 3 (2 to 4) on a 5-point scale.

## **2. Anesthesia**

Before the start of the experiment, food was withheld for 12 hours but the dogs had free access to water. No pre-anesthetic medication was administered. Anesthesia was induced with propofol (Provive® 1%; Claris, India): a dose of 8 mg/kg was prepared, then propofol was administered slowly intravenously (IV) via a pre-placed catheter until endotracheal intubation was possible. Following endotracheal intubation, anesthesia was maintained with a propofol constant rate infusion (CRI) at a rate of 0.5 mg/kg/minute until the end of the experiment. If arousal responses, such as tachypnea, tachycardia, or ear and/or tail twitching were observed, a bolus of propofol (1 mg/kg) was administered. Dogs breathed room air spontaneously during the procedure. The electrocardiogram (ECG), hemoglobin oxygen saturation (SpO<sub>2</sub>) by pulse oximetry, respiratory rate (f<sub>R</sub>) by capnometry, end-tidal carbon dioxide tension (P<sub>E</sub>'CO<sub>2</sub>), and arterial blood pressure (sBP) were continuously monitored (Datex-Ohmeda S/5®; GE Healthcare, Finland).

### **3. Positioning**

Following anesthetic induction the dogs were positioned in natural sternal recumbency with the dog's pelvic limbs flexed symmetrically as 'frog-legged', and carefully adjusted until no tension was felt in the muscles and joints of the limbs. The head was placed gently on the table, with the neck extended straight and a 5 cm thick foam padding was kept underneath the mandible to prevent an injury to the head. In order to minimize the effect of head position, the height of the occipital bone was paralleled with that of the highest point of the vertebral column. The dogs remained in this position throughout the rest of the experiment, both for radiography and whilst the subsequent laminectomy was being performed so as to minimize interference of the vertebral spread of the studied agents.

#### **4. Epidural injection of solution**

One experienced veterinarian performed the epidural injections throughout the experiments. The epidural puncture was made at the L7-S1 region with the epidural needle (19 gauge and 40 mm; Hakko medical Co., Japan) bevel directed cranially. Correct placement of the needle tip within the epidural space was confirmed with a 'pop' sensation and lack of resistance during injection. The hanging drop technique was not chosen in order to minimize the effect of solution volume. The epidural solution injected was made by adding crystalline of methylene blue (MB) dye (New Methylene Blue N<sup>®</sup>; Sigma-Aldrich Co., USA) to become a 1% solution of iohexol (Omnipaque<sup>®</sup> 350 I/ml; GE Healthcare, Ireland). A volume of 0.2 ml/kg epidural solution was administered manually into the L7-S1 epidural space at a rate of 1 ml/minute in all animals. The syringe was left attached to the spinal needle for 1 minute at the end of epidural injection. Following withdrawal of the spinal needle, the injection site was compressed for 1 minute to minimize volume loss of injected solution outside the epidural space.

## 5. Evaluation of epidural spread

With the dog remaining in sternal recumbency, and using a horizontal X-ray beam, left to right lateral radiographs were taken immediately before, and at 0, 5, 10, 15, 20, 25, 30 and 45 minutes after epidural administration in order to determine time-related epidural spread. There was no change of the dogs' position during radiography and procedures. The PH between the floor of the epidural canal of the highest vertebra, T12 or T13, and the L7-S1 injection point was measured. The angle of upward epidural slope from the injection point toward the highest vertebra was measured on the radiographs (Fig. 1). Three radiologists measured spread of contrast medium (CM) independently. Results were taken as a mean of their three readings, and a mean of dorsal and ventral spread, hence results being presented as fraction of a vertebra. The magnification factor on the radiographs, caused by the distance between the dog and the cassette, was measured by placing an iron stick of known length on the back of the dog as a reference. Measured data was then revised to take this magnification factor (0.89) into account.

Following the last of the radiographs 45 minutes after epidural injection, and whilst still under general anesthesia, dogs were bled from the carotid artery until a pulse could not be detected in the femoral artery. This procedure was to reduce bleeding during the subsequent laminectomy, which might have made detection of spread of dye more difficult. Euthanasia was then carried out by injecting 20 ml of potassium chloride solution (KCl-40<sup>®</sup> inj.; Daehan Pharmacy, Korea) IV into each dog. Euthanasia was confirmed by asystole being demonstrated both by the electrocardiograph and by no heart beat being heard by stethoscope.

Immediately following euthanasia, laminectomy was performed from the cervical to the lumbar vertebrae for visual evaluation of the spread of MB. The position of

the dogs was maintained in the same sternal recumbency for the process. The cranial spreading from the injection point was counted by approximating the number to the nearest intervertebral space to which the dye had migrated as L7 = 1, L6 = 2, L5 = 3, and so forth, up to first cervical vertebrae (C1) = 27 (Lee et al., 2001; 2004; Freire et al., 2010). The vertebra was counted only in the case that more than half of vertebra was stained. Where spread was not equal on left and right sides, the mean of the two spreads of MB was taken.

## **6. Statistical analyses**

Statistical analysis was performed by using SPSS 21<sup>®</sup> statistical program (SPSS Inc., USA). Linear regression modeling was applied to analyze the correlation between the PH and/or the angle of upward epidural slope and the cranial spread of CM and MB in the spinal canal, respectively, and to analyze the correlation between CM and MB spread. Modeling was also applied to compare body weight and BCS with cranial migration of epidurally injected CM and MB. A value of  $p < 0.05$  was considered significant. Result are given as mean  $\pm$  SD unless otherwise stated.

## Results

The mean PH and angle of upward epidural slope of 10 Beagles was  $3.8 \pm 0.8$  cm (range: 2.8 to 5.4 cm) and  $14.8 \pm 2.8^\circ$  (range: 12.0 to 21.0°) (Table 1).

In most dogs, spread of CM continued for around 20-25 minutes after epidural injection although dorsal and ventral spread were not always equal. Spread of CM reached  $12.7 \pm 5.7$  vertebrae, ranging from the C7 to the L3. Spread of MB reached at  $14.0 \pm 5.4$  vertebrae with range from the C6 to the L2. No significant relationships were found between epidural spread and body weight, and BCS. There were no correlations between PH and CM ( $R^2 = 0.08$ ) or MB ( $R^2 = 0.13$ ) spread, between the angle of upward epidural slope and CM ( $R^2 = 0.05$ ) or MB ( $R^2 = 0.02$ ) spread, respectively. However, CM and MB demonstrated proportional relationship ( $R^2 = 0.82$ ,  $p < 0.001$ ), and MB distributed more cranially than CM, although it was not significant ( $p = 0.13$ ).

Table 2 demonstrates the mean ( $\pm$  SD) cranial spread of CM at each radiographic time point. At time 0, immediately following epidural injection, CM distributed to 52% of the final maximal spread. The spread of CM decreased with time, as contrast was absorbed.

Table 1. The perpendicular height (PH), angle of upward epidural slope, maximal migration time of contrast medium (CM), the number of stained vertebra by CM and methylene blue (MB) dye from epidural injection site in dogs

Dogs (No.)	PH (cm)	Angle of slope (°)	CM		MB
			Time (minutes) of maximum migration (range from 3 assessments)	Spread (No. of stained vertebrae)	Spread (No. of stained vertebrae)
1	2.8	12.0	17.5 (15 to 20)	17.2	19.5
2	3.0	13.0	27.5 (15 to 30)	5.2	7.5
3	3.2	13.0	17.5 (5 to 30)	10.5	12.0
4	3.4	14.0	17.5 (15 to 20)	18.0	14.0
5	3.5	13.5	20.0 (15 to 20)	11.3	11.0
6	3.8	16.0	25.0 (25)	4.9	5.5
7	3.9	21.0	27.5 (25 to 30)	14.5	15.5
8	4.0	12.0	25.0 (25)	21.4	22.0
9	4.5	15.0	25.0 (10 to 30)	16.3	20.0
10	5.4	18.0	15.0 (10 to 20)	7.5	12.5

Radiographs were taken at 5 minutes intervals. CM spread was assessed by three radiologists - results are a mean of the three assessments of dorsal and ventral spread (hence times that are fractions of the 5 minutes intervals). MB is a mean of left and right spread (one assessor; hence fractions of vertebrae). Range of time of maximum spread represents differing opinions of radiologists.

Table 2. Cranial spread of contrast medium (CM) after epidural injection at each time point, and its relative ratio to maximal spread after epidural injection

Time after injection (min)	Spread of CM (Range of stained vertebrae)	Ratio of cranial spread to maximal spread (%)
0	5.9 ± 1.9 (T11 to L4)	52 ± 18
5	9.2 ± 4.4 (T4 to L4)	74 ± 14
10	11.1 ± 5.3 (T2 to L4)	87 ± 15
15	11.8 ± 5.5 (T2 to L4)	91 ± 12
20	12.0 ± 5.4 (T2 to L4)	93 ± 8
25	12.1 ± 5.4 (C7 to L3)	97 ± 4
30	11.8 ± 5.1 (C7 to L3)	91 ± 10
45	10.7 ± 6.7 (C7 to L3)	83 ± 28

Values expressed as mean ± SD (range). CM spread was assessed by 3 radiologists- results are a mean of the three assessments of dorsal and ventral spread, hence fractions of vertebrae.

## Discussion

Despite many studies examining the factors influencing efficacy of epidural analgesia in the dog (Feldman et al., 1996; Hendrix et al., 1996; Gomez de Segura et al., 2000; Gorgi et al., 2006; Freire et al., 2010), at times instances of inadequate analgesia and/or unilateral analgesia deviating from the target segments in EA still occur. Sternal recumbency is a favored position for epidural injection in order to be more certain that the needle is inserted exactly in the mid-line (Jones, 2001). In this current study, the spread of both CM and MB in sternally recumbent dogs was investigated, and a hypothesis that the effect of PH causing an upward epidural slope from the L7-S1 in dogs might, by a gravitational effect, delay or prevent cranial spread was examined.

The results of this present study showed no significant relationship between the PH and/or the angle of upward slope and epidural spread in these dogs, and was not able to prove the hypothesis. There were individual variations of the cranial spread of CM and MB which did not necessarily relate to the PH and/or angle of upward epidural slope. Although it appeared that a gravity effect was less influential on the spread of the solution in the epidural space than was expected, the possibility that it might be a significant factor in epidural hydrodynamics cannot be completely ruled out. Although the PH ( $3.8 \pm 0.8$  cm) in our sternally recumbent dogs was greater than the height of the epidural space (about 1 cm in dogs), the PH ranged only from 2.8 to 5.4 cm which was possibly too small a range significantly to affect epidural spread. Consequently, other factors might have resulted in greater influence on the epidural spread of the injectate.

In a preliminary pilot experiment, it was observed that injected solution flowed out of the injection site and stained the canal made by epidural needle, hence the

efforts to prevent this described previously. It was assumed that this phenomenon occurred due to the positive pressure, generated as fluid entered the epidural space (Rocco et al., 1997). A wide variation in the maximum epidural pressures has been observed in dogs (Iff et al., 2007). It may be that pressure changes are influenced by the compliance of the epidural space, which depends on the composition and resistance of its tissues and therefore varies between individuals (Husemeyer and White, 1980).

The cranial spread of CM (range: T11-L4) that was seen immediately after epidural injection (0 minutes, Table 2) was over 50% of the maximal spread eventually achieved. Although epidural injection was completed within 2 minutes, spread of CM continued and was maximal about 20-25 minutes after epidural injection. The positive pressure generated by the injection volume could be a major contributor to the spread in the early phase during and just after epidural injection. As mentioned above, our hypothesis was that an upward slope of epidural canal from L7 to T12 or T13 vertebra would disturb the cranial spread of solution in epidural canal in early spread phase, but CM had already distributed to the top of the epidural 'hill' during injection. Iff et al. (2007) examined the changes in epidural pressures resulting from injection of local analgesics; they demonstrated a rise in pressure of 5.5-6 kPa at injection and that this increase had not quite returned to base-line at the end of a 10 minute measurement period. Although change of the epidural pressure during and after epidural injection was not measured in this study, it is probable that the increase in epidural pressure had a greater influence on spread of solution than did position or gravity.

In some cases, the radiographs demonstrated that the spread of CM differed between the dorsal and ventral surfaces of the epidural space (Fig. 1). If gravity

influenced the epidural spread, it would be expected that CM would spread more ventrally, but no such relationship was observed. In addition, the spread of MB in the right and left side of spinal cord often differed, and spread occurred along the longitudinal epidural veins similar to that shown in cats (Lee et al., 2004). These variations of spread, which would have resulted in variable analgesia, could have been caused by deviation of epidural needle tip from the midline of epidural space and/or to anatomic structures around the spinal cord, Consequently, the contribution of the body position and gravity effects to the epidural spread in sternally recumbent dogs may be less than intrinsic factors in the epidural cavity such as anatomic structures, and the alteration of pressure during and after epidural injection.

Hydrodynamics in the epidural space have been investigated with both MB and CM (Vas et al., 2003; Lee et al., 2004; Yokoyama et al., 2004; Gorgi et al., 2006; Freire et al., 2010). In the current study, spread of CM and MB were positively related. As CM spread was identified indirectly through the radiography, the data could vary according to the radiographer, as it was difficult to distinguish readily between CM and bone opacity at times. In addition, CM was absorbed into the vascular system as time went by. However, CM based radiography is advantageous in that injected solution into the epidural space could be studied in a time-related manner. In the case of MB, epidural spread could only be observed directly after laminectomy, but range of MB spread within the epidural space could be verified in greater detail. This study showed synergic advantages of utilizing CM and MB in combination in terminal experimental condition.

## **Conclusions**

The cranial spread of injected solution into the epidural canal of sternally recumbent dogs was not significantly influenced by PH contrary to our hypothesis that gravitation effect would play a significant role in epidural spread. The study also demonstrated that rapid spread occurred almost immediately following injection, and that spread of radiographic contrast was maximal by 20 minutes. In addition, it was verified that the mixture of CM and MB was useful for surveying hydrodynamics in the epidural space in limited experimental populations where euthanasia can be carried out.

## **CHAPTER II.**

# **The Effect of Epidural Injection Speed on Epidural Pressure and Distribution of Solution in Anesthetized Dogs**

### **Abstract**

This study was performed to determine the effect of injection speed on epidural pressure (EP), injection pressure (IP), epidural distribution (ED) of solution, and extent of sensory blockade (SB) during lumbosacral epidural anesthesia.

General anesthesia was induced with propofol administered IV and maintained with isoflurane in ten healthy adult Beagle dogs. Keeping the dogs in sternal recumbency, two spinal needles connected to electrical pressure transducers were inserted into the L6-L7 and the L7-S1 epidural spaces for EP and IP measurements, respectively. Bupivacaine 0.5% diluted in iohexol was administered epidurally to each dog via spinal needle at L7-S1 space, at two rates of injection (1 and 2 ml/minute groups), with a 1-week washout period. ED was verified with computed tomography (CT), and SB was evaluated after arousal by pinching the skin with a mosquito hemostatic forceps over the vertebral dermatomes. The results were analyzed according to each injection speed, using paired t- and Wilcoxon signed-rank tests.

Mean  $\pm$  SD of baseline EP and IP values were  $2.1 \pm 6.1$  and  $2.6 \pm 7.1$  mmHg, respectively. Significant differences were observed between 1 and 2 ml/minute groups for peak EP ( $23.1 \pm 8.5$  and  $35.0 \pm 14.5$  mmHg,  $p = 0.047$ ) and peak IP ( $68.5 \pm 10.7$  and  $144.7 \pm 32.6$  mmHg,  $p < 0.001$ ). However, the median (range) of the ED, 11.5 (4 – 22) and 12 (5 – 21) vertebrae, and SB, 3.5 (0-20) and 1 (0-20) dermatomes, values of the two groups were not related to injection speed.

The EP profile during injection was measured by separating the injection and pressure monitoring lines. The increase in epidural injection speed increased the EP, but not the ED or the SB in dogs.

## **Introduction**

EA has been commonly used as a part of a balanced anesthetic protocol, for postoperative pain management in surgical cases, and to treat non-surgical pain in small animal practice (Skarda and Tranquilli, 2007; Muir et al., 2013). Unfortunately, however, inadequate analgesia was sometimes experienced including insufficient range of pain relief and SB deviating from target spinal segment, and these unexpected results have motivated research to determine the influencing factors. The factors can be divided into three main groups including physical characteristics, technical factors, and epidural anatomical and physiological factors (Lee et al., 2001, 2004). Among them, EP has been suggested as one of the epidural physiological factors since 1960s (Usubiaga et al., 1967b). In humans, several studies reported the effects of EP on ED and the extent of SB, but there have been some disagreements between authors about its significant relationship (Usubiaga et al., 1967b; Husemeyer and White, 1980; Paul and Wildsmith, 1989; Hirabayashi et al., 1990; Cardoso and Carvalho, 1998).

The pressure in the epidural space becomes positive as fluid enters the space (Rocco et al., 1997), and increased EP is a possible cause of complications related to EA in human studies (Usubiaga et al., 1967a; de Jong, 1981; Shah, 1994). Therefore, it is necessary to determine the factors influencing EP increases in order to reduce potential complications. A human study reported that injection speed significantly correlated with peak EP (Cardoso and Carvalho, 1998), but a previous study had determined no such relationship (Husemeyer and White, 1980). In a recent study of dogs, Iff et al. (2007) identified that the EP increase was not related to the duration of the injection.

Consequently, additional study is needed to solve the controversy related to the change in the EP during epidural injection that involves differences in experimental conditions, individual variations in epidural anatomy, and the resistance generated by injection force in the pressure measuring system. Therefore, this study was performed to evaluate the effect of injection speed on the change in the EP in dogs, and to examine the effect of the EP on the ED and SB.

## **Materials and Methods**

### **1. Animals**

All experimental procedures were approved by the Institutional Animal Care and Use Committee of Seoul National University (SNU-120222-2). The data were obtained from clinically healthy Beagles (five males and five females). BCS was assessed on a 9-point scale based on previously described methods (Mawby et al., 2004). Mean  $\pm$  SD body weight was  $8.7 \pm 1.6$  kg, and the median BCS was 5, ranging from 3 to 7.

## 2. Anesthesia and positioning

Food was withheld for 12 hours before the experiment, but water was provided *ad libitum*. Following premedication with acepromazine (Sedaject<sup>®</sup>; Samu Median, Korea) IV, general anesthesia was induced with propofol (4 mg/kg and 2 mg/kg increments) until endotracheal intubation was possible, and maintained with a 1.0 minimal alveolar concentration of isoflurane (Ifrane<sup>®</sup>; Hana Pharm., Korea) in oxygen using a circle system. Dogs were allowed to breathe spontaneously. Hartmann's solution (H/S<sup>®</sup>; Daihan Pharm Co., Korea) was administered at a rate of 10 ml/kg/hour IV during anesthesia.

The dorsal pedal artery was catheterized with a 22-gauge (G) over-the-needle catheter (0.9 × 25 mm; Sewoon medical Co., Korea) for measurement of arterial blood pressures. ECG, SpO<sub>2</sub> by pulse oximetry, f<sub>R</sub> by capnometry, P<sub>E</sub>'CO<sub>2</sub>, and invasive sBP were continuously monitored and recorded every ten seconds throughout the procedure on a laptop computer with a S5 data recorder (Datex-Ohmeda S/5 Collet version 4.0<sup>®</sup>; GE Healthcare, Finland).

Each dog was positioned in sternal recumbency, with the pelvic limbs extended cranially along the abdomen and chest to increase the L6-L7 and L7-S1 interspace (Di Concetto et al., 2012). The head was placed on 5 cm thick foam padding with the neck extended in a straight line. The height of the occipital bone was parallel with that of the highest point of the vertebral column to minimize the effect of head position. The dog was maintained in this position on a sliding CT table throughout the experiment.

### **3. Epidural injection and the pressure measuring system**

Bupivacaine (Bupivacaine hydrochloride<sup>®</sup>; Sigma-Aldrich, USA) 0.5% solution diluted in iohexol was prepared at a 0.2 ml/kg dose as an epidural solution for injection into the epidural space. The L7-S1 area was aseptically prepared for epidural injection. Two spinal needles (22 G × 38 mm; Tae-chang, Korea) were connected to an electrical pressure transducer (Auto Transducer<sup>®</sup>; Acemedical, Korea) via a fluid-filled and non-distensible pressure line before epidural puncture. The pressure profiles were displayed on the monitor screen and recorded on the laptop computer, which were previously mentioned. The pressure transducer was calibrated against a mercury manometer and was placed at the level of the transverse process of the last lumbar vertebra. Epidural punctures were performed at the L6-L7 and L7-S1 spaces by the same anesthesiologist, using each spinal needle with the needle bevel directed cranially (Fig. 2). As the needle penetrated the ligamentum flavum, a distinct ‘pop-ping’ sensation was felt. After the epidural puncture, a 3-minute equilibration period was allowed before baseline pressure was measured. The spinal needle inserted at the L7-S1 epidural space was connected via a three-way tap to a syringe pump (Pump 11 elite<sup>®</sup>; Harvard Apparatus, USA) that provided a constant rate injection of the epidural solution. The needle also measured IP during injection and the remaining pressure after injection. Another spinal needle at L6-L7 was used only to measure the change in EP during the same period. The epidural solution was injected twice into each dog at rates of 1 and 2 ml/minute under the same experimental conditions, with a 1-week washout period. The pressure profiles were continuously recorded for 5 minutes from the start of epidural injection.

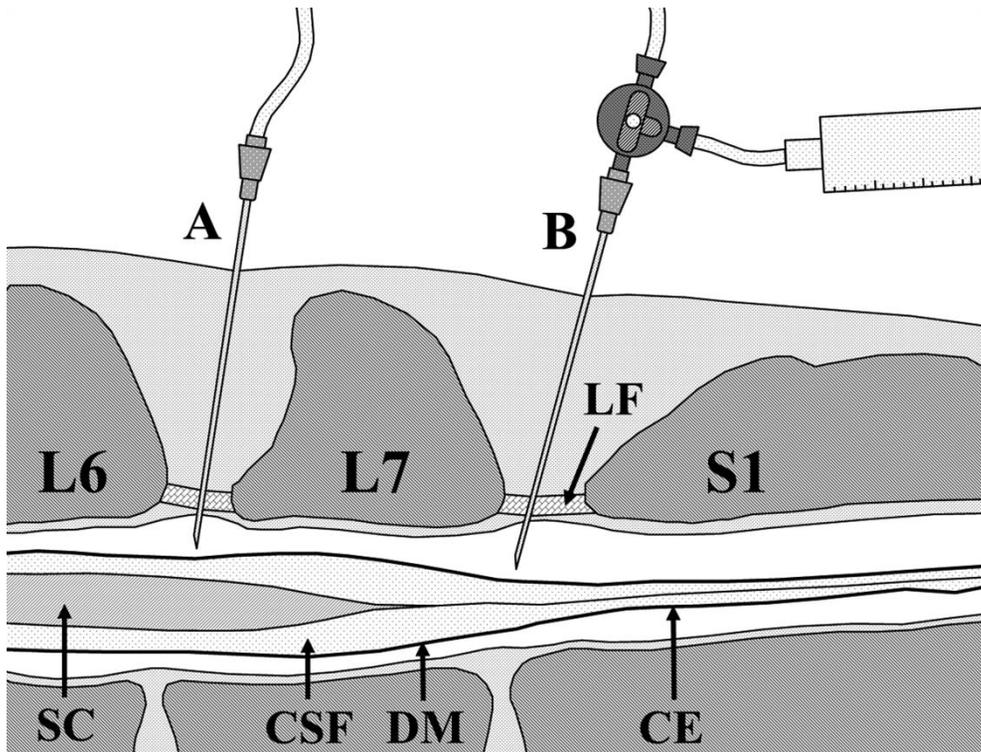


Fig. 2. Diagrammatic representation of pressure measurements in the epidural space of dogs. The two spinal needles were inserted to measure the epidural pressure (A) and injection pressure (B). The needle at L7-S1 was connected to a syringe pump via a three-way tap. CE, cauda equina; CSF, cerebrospinal fluid; DM, dura mater; L6, sixth lumbar vertebra; L7, seventh lumbar vertebra; S1, first sacral vertebra; LF, ligamentum flavum; SC, spinal cord.

#### **4. Computed tomography to evaluate epidural distribution**

Dogs were scanned using a single-slice helical CT unit (GE CT/e<sup>®</sup>; GE Healthcare, Japan), with a slice thickness of 7 mm and a pitch of 1.5 at 120 kVp and 60 mA. CT epidurographic images were obtained before injection and at 10 minutes after injection under the same CT conditions as the control and tested images, respectively. The longitudinal distribution along the epidural canal was determined using transectional images, and ED was counted by the number of distributed vertebrae from the L7 vertebra: L7 = 1, L6 = 2, L5 = 3, and so forth, up to C1 = 27 (Iseri et al., 2010). The vertebra was included when the CM was spread over more than a half of the vertebra. When there was unilateral distribution, each distribution of left- and right-sided around the spinal cord was counted separately, and the furthest spread was chosen as the ED value for the dog.

In addition, the point of the spinal needle at L7-S1 was scanned with a slice thickness of 1 mm to identify relationship between the lateral position of needle-tip and the unilateral distribution. A baseline for dividing the left and right side was drawn from the center of the spinous process to the center of the dorsal surface of the vertebral body on the transactional CT image. The data were arranged as left, right, or middle position of the needle tip, to compare with left or right unilateral and/or bilateral distribution.

## **5. Evaluation of the extent of sensory blockade**

After the CT examinations, the dogs were allowed to completely recover from anesthesia during about 20 minutes. The epidural SB was evaluated by one investigator who was blinded to the injection speed and ED. The extent of SB was assessed in three areas of the body (Lorenz et al., 2011): 1) the third bilateral pelvic toe web (L5-L7 dermatomes), 2) sacral area (L2-L5 dermatomes), and 3) the dorsal area of the ribs (thoracolumbar area; T1-L1 dermatomes). The SB at the toe web was assessed by applying hemostatic forceps, which were clamped at the first ratchet lock onto the inter-digital space of the bilateral pelvic limbs. The SB on the sacral and thoracolumbar regions was tested in a caudocranial direction, using a bilateral skin pinching method (Gomez de Segura et al., 2009). A 2-point rating scale was used for all areas: 1, present, and 2, no response. Only complete SB was assessed, and special attention was paid to ascertain that the response of the animal to the stimulus (sudden withdrawal, head turn, or vocalization) was not due to a learned behavior, but a response to a nociceptive stimulus (interdigital or skin pinch). The SB assessment was performed when the dogs were conscious; between 30 and 40 minutes after the epidural injection. The SB dermatomes were counted using the same methods as for the ED evaluation. When there was unilateral SB, each left- and right-sided dermatome from the midline of the back was counted separately, and the furthest dermatome was chosen as the SB value for the dog.

## **6. Statistical analyses**

Statistical analysis was performed using the SPSS 21<sup>®</sup> statistical program for Windows. Pressure data were reported as mean ( $\pm$  SD) values, and the ED and SB results were reported as medians (range). Normality was tested by the Kolmogorov–Smirnov test. When the descriptive data were distributed normally, a paired t-test was used to compare the matched data of two groups. The Wilcoxon signed-rank test was used if the data were not distributed normally. Overall, p value of  $< 0.05$  was considered significant.

## **Results**

Cardiopulmonary variables during anesthesia were maintained within normal ranges, and mean arterial pressure was over 60 mmHg during EA in all dogs. When the spinal needle was inserted through the ligamentum flavum, the displayed pressure rapidly increased, and then suddenly decreased in most dogs. Correct insertion of the needle tip into the epidural space was confirmed by CT imaging.

## **1. Epidural and injection pressures**

Mean baseline EP and IP values were  $2.1 \pm 6.1$  and  $2.6 \pm 7.1$  mmHg, respectively (Table 3). Mean IP profiles showed a rapid increase at the beginning of the injection and a sharp decrease after the end of the injection compared to the EP profiles in the 1 and 2 ml/minute groups (Fig. 3). Peak IP and EP measurements in the 2 ml/minute group were significantly higher than those in the 1 ml/minute group (IP:  $p < 0.001$ , EP:  $p = 0.047$ , Table 3). The waves in EP and IP were synchronized with the arterial pressure wave after injection in all dogs, and no cerebrospinal fluid (CSF) leakage was observed when the pressure tubing was disconnected from the spinal needle.

Table 3. Epidural (EP) and injection (IP) pressures before (baseline pressure) and after (peak pressure) injection, and epidural distribution (ED) and sensory block (SB)

Evaluation items		Injection speeds	
		1 ml/minute	2 ml/minute
Baseline pressure (mmHg)	EP	2.1 ± 6.1	
	IP	2.6 ± 7.1	
Peak pressure (mmHg)	EP	23.1 ± 8.5	35.0 ± 14.5*
	IP	68.5 ± 10.7	144.7 ± 32.6*
Maximum ED (vertebrae)		11.5 (4-22)	12 (5-21)
Maximum SB (dermatomes)		3.5 (0-20)	1 (0-20)

Data are mean ± SD or median (range). \*Significant difference between injection speeds ( $p < 0.05$ ).

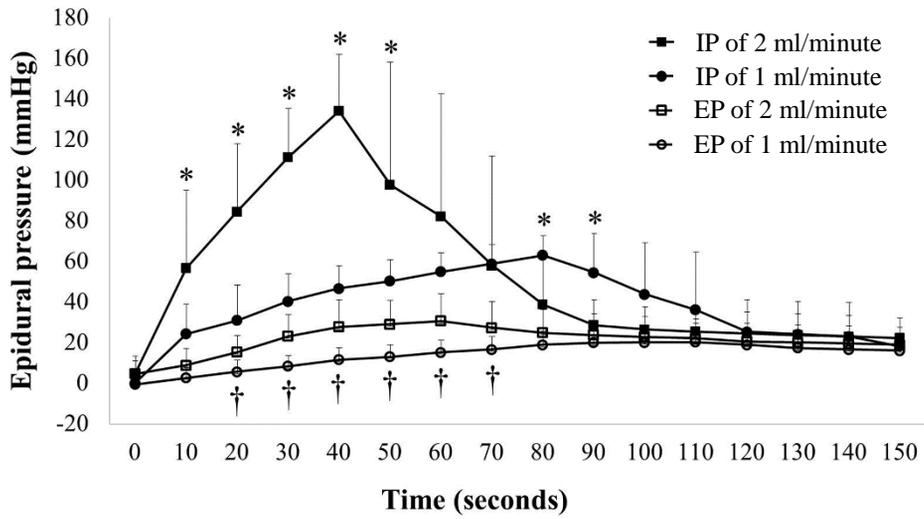


Fig. 3. Changes in injection pressure (IP) and epidural pressure (EP) during and after injection of epidural solution at 1 and 2 ml/minute. \*Significant difference between IPs ( $p < 0.05$ ). †Significant difference between EPs ( $p < 0.05$ ).

## **2. Epidurography and sensory blockade**

There was no significant difference in ED between the two groups as confirmed by CT epidurography (Table 3), but each dog had similar patterns of ED in longitudinal and transectional spread at different injection speeds. Partially unilateral distribution was observed on the cranial margin of ED in the 1 ml/ minute (right side n = 3, left side n = 6, bilateral n = 1) and 2 ml/minute group (right side n = 6, left side n = 3, bilateral n = 1). This unilateralism was compared to the biased direction (right n = 2, left: n = 17, center n = 1) of the inserted needle tip and to the peak ED, but a significant relationship was not present. Although one dog had almost unilateral distribution and SB from the injection point to the C6 vertebra, cardiopulmonary abnormalities such as bradycardia, hypotension, or apnea were not recorded during and after epidural injection.

There was individual variation in SB and no significant correlation between two groups (Table 3). A significant correlation between matched ED and SB was observed ( $p < 0.001$ ).

## **Discussion**

Several studies have reported that EP measured via a needle inserted into the epidural space was changeable by posture, pregnancy and epidural injection in both humans and animals (Messih, 1981; Lee et al., 2002; Iff et al., 2007). During EA, the epidural injection induces a substantial increase in EP, and it has been suggested as an influencing factor on ED of injected fluid (Usubiaga et al., 1967b; Hirabayashi et al., 1990). In addition, excessive increment of EP is a possible cause of complications related to EA in human studies (Usubiaga et al., 1967a; de Jong, 1981; Shah, 1994). For adequate epidural analgesia with minimal complication, it is necessary to prevent a sudden and excessive alteration of EP, and to determine the influencing factors on EP increment during injection.

Three main factors have been suggested to influence positive pressure generated by injection of a solution into the epidural space: 1) volume, 2) injection speed, and 3) epidural anatomical characteristics (Bengis and Guyton, 1977; Hirabayashi et al., 1990; Cardoso and Carvalho, 1998; Lee et al., 2002). In general, the injected solution increases pressure in a restricted space like the epidural space, and the severity of it necessarily depends on the volume and speed of solution injected. However, a previous study in humans reported that peak EP is not related to injection volume (Paul and Wildsmith, 1989). A more recent study determined a significant relationship between volume and remaining pressure after injection in humans (Cardoso and Carvalho, 1998). Although the injection volume may increase EP, it may be not a critical factor governing the peak pressure in the epidural space.

Injection speed under the same volume condition has been suggested as a major factor associated with peak EP. A previous human study reported that increased EP was not related to injection time in pregnant women (Husemeyer and White, 1980),

but a later study indicated that peak pressures were correlated with the speed of injection of a lidocaine solution (Cardoso and Carvalho, 1998). In dogs and cats, only one clinical guideline is available for injection time, stating that more than 30–60 seconds should be taken to inject epidural anesthetic agents (Jones, 2001). Iff et al. (2007) reported the EP profiles were generated by injection over 30 or 90 seconds with a variation in EP and no significant difference between the peak EP and injection time in dogs. In the present study, injection of 0.2 ml/kg at rates of 1 and 2 ml/minute resulted in 60 and 30 seconds for 1 ml per 5 kg, respectively, and the peak EP was significantly related to injection speed ( $p = 0.047$ ). Comparing with the previous study of Iff et al. (2007), the use of constant rate injection would be necessary to control the peak EP during epidural injection. In addition, in large or obese dogs, for which the calculated volume of epidural fluid is large, maintaining the guideline of 30-60 seconds would result in a more rapid administration and a secondary EP increment. Consequently, a constant rate injection should be recommended as a standard procedure to prevent the excessive increase of EP during EA. Although a maximum safe EP level has not been reported, a slower injection with constant rate would be more suitable for high risk groups of EP increase by injection, such as lumbar spinal stenosis, pregnancy, or risk for intracranial hypertension (Messih, 1981; Hilt et al., 1986; Takahashi et al., 1995).

The anatomical characteristics of the epidural canal have also been suggested as a factor influencing peak EP. The epidural canal has a compliance, which depends on the composition and resistance of the tissue in the epidural space, and a leaking space at the intervertebral foramina (Rocco et al., 1997). These characteristics have been proposed as causes of wide variations observed in peak EP during injection, and as reasons for the lack of correlation between peak EP and injection speed (Husemeyer

and White, 1980; Iff et al., 2007). However, the significant correlation between EP and injection speed in this study minimizes the effect of epidural compliance on its correlation. In fact, the experiment in the present study was duplicated in the same dog with different injection speeds in order to minimize individual variations in epidural anatomy and to identify the conditions which generated the significant relationship between EP and injection speed.

In most previous studies, epidural injection and EP measurement were performed using only one spinal needle (Husemeyer and White, 1980; Paul and Wildsmith, 1989; Rocco et al., 1997; Cardoso and Carvalho, 1998; Iff et al., 2007). However, when EP is measured at the injection site with this method, falsely high pressure could be generated by the resistance against the injection force by the needle, the three-way tap and the needle tip in an enclosed epidural tissue. Because it was thought that this falsely high pressure may disrupt the verification of EP alteration according to injection speed, the two spinal needles were used for separating the injection line from pressure monitoring line in this study. This was particularly important in this study, because the high viscosity of epidural solution like CM might increase resistance during injection through the small diameter spinal needle.

The effect of peak EP on epidural analgesia was not identified in this study. When a fluid easily flows along the epidural canal, the solution may spread in association with peak EP related to its injection speed. However, the epidural space is a true potential space, which is mostly filled with connective tissue, fat, and a venous plexuses (Newell, 1999), and is only apparent when the dura mater is artificially separated from the overlying vertebral canal by the injection of fluid (Parkin and Harrison, 1985). In addition, Hogan (2002) reported that the epidural solution spread from an area of high injected pressure to the margins of distribution where fluid

pressure is low via the various passages among the epidural tissue according to the subtle forces compressing their opposing surfaces. Although elevated EP generated by the volume of injected solution plays a major role in the ED of that solution, the effect of peak EP on ED and SB would be restricted by epidural structures' impeding the flow of epidural solution. In a study examining influence of volume and injection speed on EA in human patients, it had been reported that the injected solution might be mainly spread by remaining EP after the termination of injection more than peak EP related to its injection speed (Cardoso and Carvalho, 1998).

Computed tomography provides better resolution than radiography for hydrodynamic studies of an injected epidural solution, as CT shows not only the longitudinal distribution along the epidural canal, but also the transectional distribution around the spinal cord (Iseri et al., 2010). Sternal or dorsal recumbency after epidural injection in dogs has been recommended to facilitate an even distribution and bilateral blockade (Torske and Dyson, 2000, Jones, 2001). Nonetheless, in almost all dogs of this study, partial unilateral distribution and SB were confirmed at the most cranial dermatomes. One proposed mechanism for this abnormality in humans is unilateral distribution caused by the needle tip position (Whitlock et al., 2007). However, there was no relationship between ED and the location of the needle tip in the dogs of this study. In an epidural study using human cadavers, similar ED was reported in that the passage of ink around the dura was completely circumferential near the injection sites in most cases, but it was typical to see nonuniform spread away from injection sites (Hogan, 2002). The reason of uneven distribution might be too low fluid pressure to pass between the tissues in the epidural space (Hogan, 2002).

In the results of this study, although a significant relationship between ED and SB was observed, there was a substantial gap between mean ED and SB. The analgesic area is changeable according to type of nociceptive stimuli and scale of pain assessment, and evaluating the blocked area against an intense stimulus such as pinching in this study would reduce the extent of SB. A study where bupivacaine was injected epidurally, the extent of SB was changeable according to the passage of time, and peak ED was generated within 20 minutes from epidural injection (Freire et al., 2010). The author tried to minimize the time gap between epidural injection and pain test for verification of the peak ED. In the present study, however, general anesthesia was essential to measure the EP during and after epidural injection, to maintain the sternal position during ED of injected solution, and to scan distribution of the injected solution with CT. Consequently, assessment of response to nociception had to be delayed until the dogs recovered from anesthesia, and the extended time gap also might have considerably influenced differences between the extent of ED and SB.

## **Conclusions**

The EP alteration by constant rate injection was ascertained without the resistance of the pressure measuring device by separating the injection and pressure monitoring lines. The peak EP was directly correlated with the injection speed of the epidural solution in dogs, but not ED and SB.

## CHAPTER III.

# The Volume Effect of Lidocaine on Thoracic Epidural Analgesia in Conscious Beagle Dogs

### Abstract

This study was performed to evaluate the volume effect of local anesthetic solution on thoracic epidural analgesia in dogs.

A catheter was inserted into the seventh thoracic epidural space using a L7-S1 approach, and secured with suture under total IV anesthesia with propofol in five healthy adult Beagle dogs. Each dog was administered 4 volume treatments (0.05, 0.10, 0.15 and 0.20 ml/kg) of 2% lidocaine via the catheter at 12 hour intervals. In every treatment, dogs were re-anesthetized with propofol (6 mg/kg IV) and isoflurane, and received iohexol at each volume to visualize the ED through CT. Three hours after epidurography when dogs had recovered from anesthesia, the appropriate volume of lidocaine was injected through the catheter, and SB in dermatomes was evaluated by pinching with a mosquito forceps. Results were presented as mean (range), and the volume effect on ED and SB was analyzed with one-way Kruskal-Wallis ANOVA (analysis of variance).

In proportion to volumes (0.05, 0.10, 0.15, and 0.20 ml/kg), there were significant increases in the extent of ED from 7.4 (5.5-9.0) to 10.4 (8.0-12.0), 13.2 (12.5-13.0), and 15.2 (13.0-18.0) vertebrae, respectively,  $p < 0.001$ , and in SB from 2.7 (1.0-5.0) to 6.8 (4.5-10.5), 9.9 (6.5-13.0), and 13.1 (11.0-15.0) dermatomes, respectively,  $p <$

0.001. Unilateral ED and SB were observed in all treatments with various grades, and this distribution was more frequent in the low volume treatments. In the high volume treatments, temporary complications including Horner's syndrome, ataxia, paraplegia, depression, stupor, and intermittent cough occurred often.

The increase in volume of local anesthetic solution improved SB by resulting in more consistent bilateral dermatome blockade as well as an extended blockade. However, caution should be exerted, as higher volume injections of lidocaine caused side effects in all dogs.

## **Introduction**

Thoracic epidural analgesia (TEA) is a regional anesthesia-based technique used to relieve thoracic pain after surgery or during critical care in small animals and humans (Wetmore and Glowaski, 2000; Hansen, 2001; Manion and Brennan, 2011). Concern that TEA may induce side effects potentially unsafe for the patient has delayed acceptance of the technique into routine use. In humans, further studies of TEA have supported its use to reduce the incidence of respiratory complications following various types of surgery (Ballantyne et al., 1998). In small animals, use of an epidural catheter to induce TEA has been reported (Wetmore and Glowaski, 2000; Hansen, 2001), but there is little published researches focusing on TEA in veterinary compared to human medicine.

Thoracic epidural injection of local anesthetic agents is commonly performed via an epidural catheter. Insertion of an epidural catheter facilitates management of continuous pain by easy administration of repetitive bolus injections or constant infusion (McLeod and Cumming, 2004). In humans, intermittent bolus injection is preferred compared to constant infusion, because a bolus injection results in more extensive ED and less regression of SB (Wong et al., 2006). However, the risks of respiratory depression (Etches et al., 1989) and hemodynamic instability (Shuman and Peters, 1976) have been documented and associated with the use of bolus epidural injections. Therefore, choice of a bolus dose that achieves adequate analgesia with minimal complications is important.

Epidural drugs are typically administered to small animals in a volume of 0.10-0.22 ml/kg (Wetmore & Glowaski, 2000; Hansen, 2001). However, the relationship between volume and the effect of local anesthetics administered at the thoracic level has not been characterized in dogs. Therefore, this study was performed to determine

the effect of injectate volume on TEA with catheter using the L7-S1 approach in dogs.

## **Materials and Methods**

All experimental procedures were approved by the Institutional Animal Care and Use Committee of Seoul National University (SNU-130306-1). Data were obtained from five male Beagles that were clinically healthy based on physical examination, radiographic imaging (chest and spine views) and blood tests (complete blood cell count and serum chemistries). BCS was assessed on a 9-point scale based on methods described previously (Mawby et al., 2004). The mean  $\pm$  SD body weight was  $9.7 \pm 1.3$  kg, and the median BCS was 5 (range, 5-6). Food was withheld for 6 hours with free access to water before anesthesia. Before the experimental procedure, hair was clipped over the cephalic vein, L7-S1 area and bilaterally over the thorax for IV catheterization, epidural puncture, and assessment of blocked dermatomes, respectively.

## 1. Epidural catheterization

A 22 G over-the-needle catheter was inserted into the cephalic vein. Propofol was administered IV up to 6 mg/kg until endotracheal intubation was possible, and then supplemented by repeated incremental IV boluses at 2 mg/kg as required. The dog was allowed to breathe spontaneously, and Hartmann's solution was administered at a rate of 10 ml/kg/hour IV during the procedure. ECG, SpO<sub>2</sub>, f<sub>R</sub>, P<sub>E</sub> CO<sub>2</sub>, sAP were continuously monitored. The dogs were positioned in sternal recumbency with the pelvic limbs extended cranially along the abdomen and thorax. Skin over the L7-S1 area was prepared for aseptic puncture. A Tuohy needle (17 G and 9.84 cm; Arrow International Inc., USA) with the bevel directed cranially was inserted between the seventh lumbar (L7) and first sacral vertebra (S1). Placement of the tip of the needle in the epidural space was assessed by a pop-sensation and no-resistance to injection of 0.9% saline (1 ml; N/S<sup>®</sup>; Daihan Pharm., Korea). The epidural catheter (REF EC-05000 TheraCath<sup>®</sup>; Arrow International Inc., Ireland) was equipped with an imbedded coiled spring and a stylet wire to prevent collapse and kinking during advancement along the epidural canal. The catheter was inserted into the epidural space via the Tuohy needle using an aseptic technique, then the dog was repositioned in lateral recumbency, and the catheter was advanced cranially up to the level of the seventh thoracic vertebra (T7). Correct placement of the catheter tip was confirmed by lateral radiograph after removing the stylet from the catheter. Furthermore, inadvertent insertion of the catheter into a venous sinus or intrathecal space was verified by negative withdraw of blood or CSF, respectively. After completing the installation, the catheter was fixed on the dorsal skin with sutures and a sterile drape (Ihoban<sup>™</sup> 2; 3M Health Care, USA), and fully filled with 0.5 ml of 0.9% saline that corresponded to a previously measured catheter volume. At the end of the procedure,

animals were allowed to recover from anesthesia and observed for 24 hours for catheter dislodgement or any acute neurologic signs resultant from catheter placement, such as epidural hematoma or nerve damage (Giebler et al., 1997; Swalander et al., 2000), before continuing to the next phase of study.

## **2. Epidurography**

Four different volumes of lidocaine (2%; Daihan Pharm., Korea) were administered through the epidural catheter in each dog at 12 hour intervals. Three and a half hours before each lidocaine injection, general anesthesia for epidurography was induced with propofol (6 mg/kg, IV) until endotracheal intubation was possible, and maintained with isoflurane (1.5 minimum alveolar concentration) in oxygen delivered through a rebreathing circle system. The dog was allowed to breathe spontaneously, and Hartmann's solution was administered at 10 ml/kg/hour IV during anesthesia. Additionally, ECG, SpO<sub>2</sub>, f<sub>R</sub>, P<sub>E</sub>CO<sub>2</sub>, and sAP were monitored continuously. The dog was positioned in sternal recumbency on a sliding CT table, and epidurography was performed from the occipital bone to sacral bone, using a single-slice helical CT unit with a slice thickness of 7 mm and a pitch of 1.5 at 120 kVp and 60 mA. Iohexol was administered manually through the epidural catheter at a rate of 1 ml/minute using the same volume as the volume of lidocaine to be subsequently evaluated. Scanning was performed twice, before injection and immediately after injection of iohexol under the same CT conditions as the control and tested images, respectively. The distribution of iohexol in the epidural space was determined using transectional images, and the extent of longitudinal distribution along the epidural canal was measured by counting the number of stained vertebrae. A vertebra was not counted if less than half the vertebral length was stained. When the pattern of distribution was uneven and asymmetric, a baseline for dividing the left and right side was drawn from the center of the vertebral dorsal spinous process to the center of the dorsal surface of the vertebral body on the transactional CT image, the extent of left- and right-sided ED around the spinal cord were counted separately based on the line, and the two values were averaged. After

completing the epidurography, the catheter was flushed with 0.5 ml of 2% lidocaine, and the animals were allowed to recover from anesthesia.

### **3. Epidural blockade**

The lidocaine injection was delayed for 3 hours after epidurography so that every dog was completely aroused from isoflurane anesthesia and to eliminate iohexol from the epidural space. Four volume treatments of lidocaine were 0.05, 0.10, 0.15, and 0.20 ml/kg (treatments V1, V2, V3, and V4, respectively), and the order of treatments for every dog was established randomly according to a Latin square design. Every injection was manually performed at a rate of 1 ml/minute with the dog in standing position without sedation. Epidural blockade was evaluated by one experienced investigator who was blinded to the injected volume and CT results. The SB was assessed on dermatomes in the following four areas of the body: cervical area (C1-C7), dorsal area of the ribs (thoracolumbar area; T1-L1 dermatomes), sacral area (L2-L5 dermatomes), and bilateral pelvic limbs (L5-L7 dermatomes) (Lorenz et al., 2011). The test was performed cranially and caudally from the T7 dermatome using skin pinching, which was bilaterally performed based on the vertebral dorsal spinous process with a mosquito hemostatic forceps (H112-22012<sup>®</sup>; Hermann Medizintechnik, Germany) at the first ratchet lock. A 2-point rating scale was used for all areas: 1, present, and 2, no response. Only complete blockade was assessed, and normal response to painful pinching was ascertained by a sudden withdrawal response, head turn and/or vocalization, not a learned behavior (Gomez de Segura et al., 2009). The test was performed immediately after the end of lidocaine injection and repeated every 5 minutes until there was no further increase in the area blocked. The extent of SB was measured by counting the number of dermatomes blocked. The extent of left- and right-sided SB was averaged when there was uneven and asymmetric blockade. After completing the SB assessment, the catheter was flushed with 0.5 ml of iohexol.

The epidural catheter was removed after all treatments, and the total duration of the epidural catheter *in situ* was not more than 72 hours. Postanesthetic complications related to TEA were then assessed during the following 24 hours. After that, 0.2 ml/kg of 2% lidocaine was administered IV to all dogs for verification of a systemic effect, and behavior changes were observed for 30 minutes.

#### **4. Statistical analyses**

The statistical analysis was performed using the SPSS 21 statistical program for Windows, and all tests used a significant level of 5%. ED and SB data were presented as means (range) and differences in ED and peak SB were analyzed by one-way Kruskal-Wallis ANOVA with a within-subject volume factor. Post hoc analysis of six pairwise comparisons among four volume treatments was performed using Mann-Whitney test and a sequentially rejective Bonferroni-Holm method; the p values of multiple comparisons were arranged in an ascending order, and Bonferroni-Holm rejective criteria related to them for a significant of 5% were 0.0083, 0.0100, 0.0125, 0.0167, 0.0250 and 0.0500. In addition, the peak SB was compared with the matched ED data using Spearman rank correlation separately by treatments.

## **Results**

The process of epidural catheterization and epidurography was completed within 30 minutes, and most cardiopulmonary variables were stable during anesthesia. Several episodes of transient tachycardia, tachypnea and muscle twitching were observed during advancement of the epidural catheter along the epidural canal. Some coiling of the catheter was detected by radiography when there was resistance against smooth advancement of the catheter. Placement of the catheter tip at the T7 level without coiling of the catheter was achieved by gentle repeated back and forth movement of the catheter. No leakage of CSF or blood occurred through the installed catheter, and no complications related to epidural catheterization were observed during or after the experimental procedure except for traces of blood on the catheter in some dogs after removal.

## 1. Epidurography and epidural blockade

Onset of SB was within 5 minutes after epidural injection of lidocaine, and the extent of SB reached a peak within 20 minutes in all treatments. The peak SB increased in proportion to the injected volume, and the post hoc analysis revealed significant differences between treatments V1 and V3 ( $p = 0.008$ ), treatments V1 and V4 ( $p = 0.008$ ), treatments V2 and V4 ( $p = 0.008$ ), and treatments V1 and V2 ( $p = 0.016$ ), but insignificant between treatments V3 and V4 and treatments V2 and V3 (Table 4). The ED also increased according to the injected volume, and the post hoc analysis revealed significant differences between treatments V1 and V3 ( $p = 0.008$ ), treatments V1 and V4 ( $p = 0.008$ ), treatments V2 and V3 ( $p = 0.008$ ), and treatments V2 and V4 ( $p = 0.008$ ), but insignificant between treatments V1 and V2 and treatments V3 and V4 (Table 4). Significant correlation between peak SB and ED was not observed in all treatments (Table 4).

The raw data of ED and SB are expressed on two maps (Figs. 4 and 5). These maps were asymmetric and uneven in all treatments with various grades, and this asymmetry was more clearly observed in the low volume treatments. In particular, V1 treatment (the lowest volume) resulted in unilateral blockade in all dogs (Fig. 5), and in three dogs the target segment (T7) was not blocked, even though T7 was stained following iohexol injection (Fig. 4). In addition, dogs with unilateral blockade were observed to have unilateral distortion of the rib cage by muscle relaxation of the blocked side.

On the epidurographic transverse CT images along the epidural canal, relatively large epidural capacity was observed around the cervicothoracic junction, and relatively large accumulation in the epidural space and intervertebral leakage of iohexol were observed from C6 to T2 in V4.

Table 4. The extent of epidural distribution (ED) and sensory blockade (SB) according to the injected volume of contrast medium (CM) and lidocaine, respectively, and the correlation between ED and SB

Treatment	Volume (ml/kg)	ED of CM (Vertebrae)	SB of lidocaine (Dermatomes)	Spearman rank correlation
V1	0.05	7.4 (5.5-9.0)	2.7 (1.0-5.0)	rho = -0.526 p = 0.362
V2	0.10	10.4 (8.0-12.0)	6.8 (4.5-10.5) *	rho = 0.400 p = 0.505
V3	0.15	13.2 (12.5-13.0) *†	9.9 (6.5-13.0) *	rho = -0.316 p = 0.604
V4	0.20	15.2 (13.0-18.0) *†	13.1 (11.0-15.0) *†	rho = -0.154 p = 0.138

Data are mean (ranges). \*Significant difference from V1 ( $p < 0.05$ ). †Significant difference from V2 ( $p < 0.05$ ).

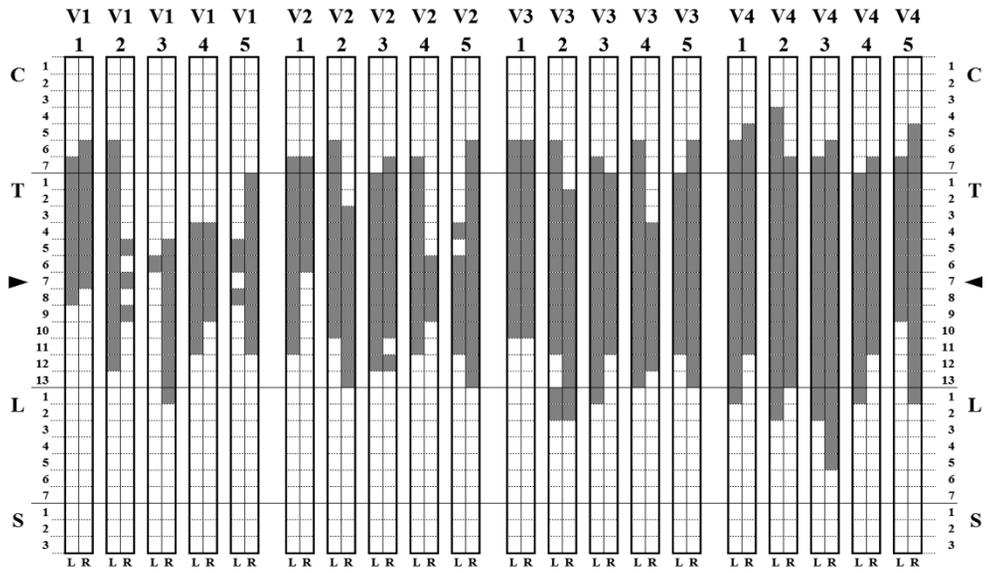


Fig. 4. Map of epidural distribution of iohexol injected through an epidural catheter at the seventh thoracic vertebra (►) in five dogs at 0.05, 0.10, 0.15, and 0.20 ml/kg (V1, V2, V3, and V4, respectively). Shaded area represents iohexol distribution. C, cervical vertebrae; T, thoracic vertebrae; L, lumbar vertebrae; S, sacral vertebrae; R, right side; L, left side.

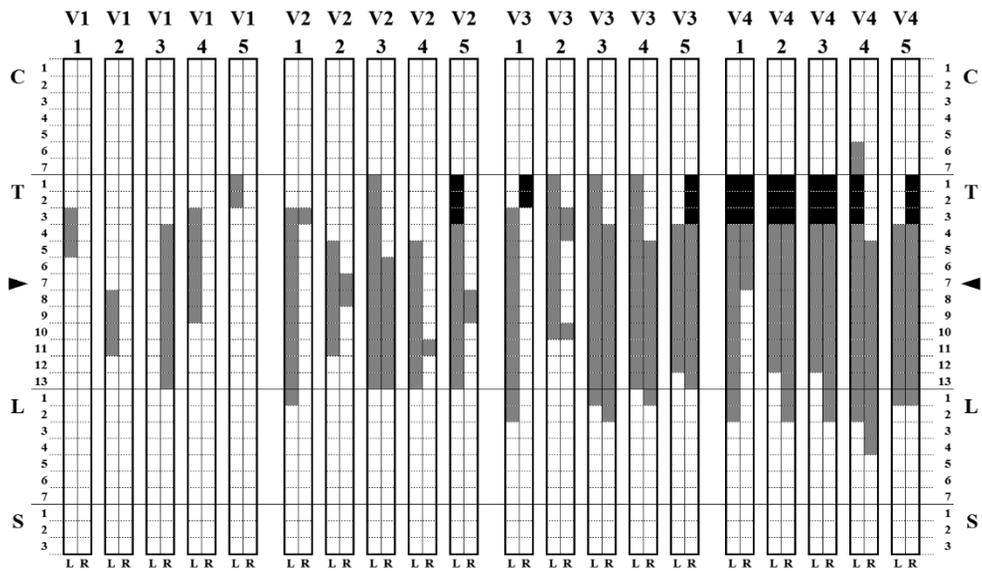


Fig. 5. Map of dermatomes blocked after administration of lidocaine via an epidural catheter at the seventh thoracic vertebra (▶) in five conscious dogs at 0.05, 0.10, 0.15, and 0.20 ml/kg (V1, V2, V3, and V4, respectively). Shaded areas represent sensory blockade and black areas are blocked dermatomes associated with occurrence of Horner's syndrome. C, cervical vertebrae; T, thoracic vertebrae; L, lumbar vertebrae; S, sacral vertebrae; R, right side; L, left side.

## **2. Complications**

Neurologic signs occurred in V2, V3, and V4 during the SB test. The signs included Horner's syndrome (unilateral or bilateral eyes), paraplegia (without withdrawal reflex), ataxia (staggering gait), depression (closed eyes and head down in a sitting posture), and stupor (dissociative-like reaction in lateral recumbency; that was very similar to sedation or light general anesthesia using a dissociative agent) (Table 5). These neurologic signs appeared within 5 minutes of the lidocaine injection. Most resolved within 30 minutes of injection, except Horner's syndrome, which persisted for about 1 hour. Although the signs varied, increased severity and frequency were observed in the higher volume treatments (Table 5). All dogs in V4 developed Horner's syndrome, and an intermittent cough was observed for about 2.5 hours after lidocaine injection. Almost all dogs with Horner's syndrome had blockade of the T1, T2 and T3 dermatomes on the same side of the syndrome (Fig. 5). Despite these neurologic complications, pain reaction (howling or sudden head up) in response to noxious stimulation was observed and distinguished. No other neurologic signs or permanent complications were observed.

No change in behavior was observed following IV injection of lidocaine, and all dogs recovered without further complications.

Table 5. Frequency (the number of dogs affected in each treatment) of temporary complications after thoracic epidural injection of lidocaine through an epidural catheter at the seventh thoracic vertebra in five conscious dogs at 0.05, 0.10, 0.15, and 0.20 ml/kg (V1, V2, V3, and V4, respectively)

	Treatments			
	V1	V2	V3	V4
Ataxia	0/5	3/5	3/5	0/5
Cough	0/5	0/5	0/5	4/5
Depression	1/5	1/5	0/5	0/5
Horner's syndrome	0/5	1/5	2/5	5/5
Paraplegia	0/5	1/5	3/5	4/5
Stupor	0/5	0/5	1/5	3/5

## **Discussion**

The injected volume of local anesthetic solution influences the spread within the epidural space, and the extent of analgesia (Kaneko and Iwama, 1999). Choice of dosage is essential to achieving adequate blockade. In small animals, epidural drugs are generally administered in a volume of 0.10-0.22 ml/kg using epidural catheter techniques, but there is little information about the relationship between volume and analgesic effects (Wetmore and Glowaski, 2000; Hansen, 2001). In addition, this dose recommendation is not adjusted according to the site where the drug was administered, such as the thoracic or lumbar vertebral section. The length of the lumbar vertebral column is relatively short, and the dimensions of the lumbar epidural space are fairly constant. However, the thoracic part of the spinal column encompasses more than half the length of the entire spine, and the thoracic vertebrae and epidural space vary greatly in shape and size (Dyce et al., 2002). Considering this variance in anatomy, the distribution of neural blockade may be altered according to the vertebral level where the drug is administered (Visser et al., 2008). Therefore, this authors focused on estimating the volume of local anesthetic solution that would be most effective for TEA in dogs.

The spread of epidural analgesia along the vertebral canal has been commonly estimated by using an injected volume of local anesthetic solution per dermatome anesthetized (Iwama et al., 2000). In this study, the extent of dermatomal blockade produced by four different volumes was ascertained for TEA. The required volume per dermatome blocked was about 0.02 ml/kg with a total volume of 0.20 ml/kg suitable for blocking the entire thoracic section, and these results will help to predict segmental dose requirements on TEA of dogs. In a study in humans where local anesthetic solution was injected epidurally at high-, mid- and low-thoracic levels,

different patterns of SB were found for cephalad and caudal distributions from the injection site, but the total number of dermatomes blocked was unrelated to the level of injection (Visser et al., 1998). Considering this report, further study is needed to ascertain whether these patterns according to injection level can be applied to dogs as well as humans.

Uneven blockade and distribution commonly accompany epidural catheter injection techniques (Hogan, 1999). Likely explanations for these problems include lateral placement of the tip of the epidural catheter (Hogan, 1999), the presence of a posterior midline septum (Asato and Goto, 1996), air bubbles (Dalens et al., 1987), and epidural fibrous barriers (Fukushige et al., 1997), all of which restrict the usefulness of drug administration via an epidural catheter. In the present study, although the cause of uneven blockade was not identified, the non-homogeneity of epidural blockade occurred most commonly in the low volume treatments. Similarly, Hogan (2002) reported that in humans unpredictable epidural analgesia occurs due to nonuniform distribution of the solution in the epidural space, and the nonuniform distribution is marked when the injected volume is small. Because the epidural space, which is a true potential space primarily filled with connective tissue, fat, and venous plexuses, is only apparent when the dura mater is artificially separated from the overlying vertebral canal by the injection of fluid (Parkin and Harrison, 1985; Newell, 1999), epidural solution spreads via potential passages among the tissues according to the subtle forces compressing their opposing surfaces by fluid pressure of injected volume from an injected area of high fluid pressure to the margins of distribution where fluid pressure is low (Hogan, 2002). Thus, if the volume of epidural solution is too low to squeeze in a closed passage with high resistance, the solution selectively flows through a less resistant passage, which explains the mechanism of uneven

distribution and blockade in the low volume treatments in this study. Treatment V4 was the highest volume (0.20 ml/kg) and produced relatively homogenous blockade as well as the most extensive blockade over the whole thoracic section compared to other treatments. In contrast, several dogs in V1 administered the lowest volume (0.05 ml/kg) showed that even the target segment (T7) was not blocked. In a clinical review of small animals subjected to the epidural catheter technique, additional analgesia or sedation was provided in 131/182 patients (72%) due to inadequate analgesia (Hansen, 2001). Although the cause was not presented, uneven blockade by insufficient volume could be considered a reason for additional pain management. Consequently, when injectate volume is selected in TEA, the homogeneity of blockade as well as the desired extent should be considered for adequate analgesia and the use of a dose  $< 0.05$  ml/kg should be avoided. Furthermore, additional pain management may have to be considered in dogs receiving a volume  $< 0.20$  ml/kg.

Epidural bolus injection with a large volume of local anesthetic solution could cause excessive cranial spread, and has been considered as a cause of complications including cardiovascular instability (Shuman and Peters, 1976) and respiratory depression (Etches et al., 1989). These complications have often been reported in even lumbar epidural analgesia (Blass and Shires, 1986; Iff & Moens, 2008), and the concern for excessive blockade of the thoracic spinal cord has delayed the clinical application of TEA. To avoid the potential complications due to excess volume, this study investigated four different volumes for thoracic epidural injection, with a maximum volume of 0.22 ml/kg, and with a maximum volume of approximately 6 ml for any size dog, as previously suggested (Wetmore and Glowaski, 2000). However, despite this consideration, various temporary complications were noted according to injected volume including Horner's syndrome, ataxia, paraplegia,

depression, stupor, and intermittent cough. These TEA complications have not been reported in small animals, with the exception of Horner's syndrome (Franci et al., 2012).

Horner's syndrome (miosis, ptosis of upper eyelid, enophthalmos, and protrusion of the nictitating membrane in dogs) indicates a problem in the sympathetic nervous system that originates in the upper thoracic cord (T1, T2, and T3 in dogs) (Maggs et al., 2012), and the syndrome was reported as a complication of TEA in humans and small animals (Quinot et al., 1989; Franci et al., 2012). The most logical reason for this complication is direct blockade by excess cephalad spread of local anesthetic up to the upper thoracic segment (Biousse et al., 1998). This theory was also supported by our results, because the T1-T3 dermatomes were blocked in almost all dogs with Horner's syndrome, which was found on the same side of the blocked T1-T3 in the SB map. The incidence of Horner's syndrome varied in previous studies related to TEA. In a study examining the adverse effects of TEA in 1,071 human patients, Horner's syndrome was not reported (Scherer et al., 1993). In contrast, a human study in which a solution of 0.5% bupivacaine was administered by continuous infusion for postoperative analgesia after thoracotomy, 22 of 167 patients developed Horner's syndrome (Quinot et al., 1989). In addition, there was only one case report of a dog that showed temporary unilateral Horner's syndrome among three dogs on TEA using a paramedian approach (Franci et al., 2012). In this study, Horner's syndrome was observed in 40% of all procedures and 100% in V4. This incidence was significantly higher compared to that in previous studies. In addition, several V2 and V3 dogs showed various grades of anisocoria suggesting partial Horner's syndrome although it was not recorded. Aronson et al. (2000) stated that Horner's syndrome might often be unrecognized, although it is probably a rare complication

of TEA. Horner's syndrome goes unrecognized in many patients when it occurs bilaterally. Without the obvious asymmetry, miosis may be attributed to the narcotic effect, and ptosis may not be appreciated in an otherwise sedated individual. Furthermore, it is speculated that general anesthesia or systemic depression can disrupt eye examinations and the diagnosis of Horner's syndrome. Consequently, it is possible that the actual incidence of Horner's syndrome in TEA is underreported. Similarly, other temporary complications (ataxia, paraplegia, depression, stupor, and intermittent cough) observed in this study may have been overlooked due to concurrent conditions such as general anesthesia, systemic depression, or orthopedic and neurologic diseases in patients undergoing TEA.

The mechanism of action of epidural analgesia produced by local anesthetic agents results from regional blockade of the paravertebral nerve, the distal nerve root within the CSF in the subarachnoid space, and the spinal cord (Torske and Dyson, 2000). Regional blockade of motor efferents may partially explain motor abnormalities of temporary TEA complications. However, recent studies have suggested sedative and subanesthetic effects due to epidural local anesthetic agent delivery to the brain (Hodgson and Liu, 2001; Xiao et al., 2002; Ishiyama et al., 2005; Kim et al., 2010), which could be a better explanation for the mechanism of temporary central nervous system (CNS) signs related to the brain in the present study. Thoracic epidural lidocaine could be delivered to the brain via three potential pathways, including excessive cranial spreading in the epidural space, systemic circulation by vascular absorption (Lemke, 2007), cranial diffusion via CSF in the subarachnoid space (Hodgson and Liu, 2001; Xiao et al., 2002; Kim et al., 2010), or their combinations. However, the effect of epidural and systemic pathways were thought to be minor in this study, because the cranial border of the EB and SB did not reach the brain in the

maps, and there was no behavior change after IV injection of lidocaine at the highest dose (4 mg/kg) of the volumes evaluated. In addition, the concentration of local anesthetic within the CSF after epidural injection is significantly higher than plasma concentrations when measured at the same time (Wilkinson and Lund, 1970). Therefore, the primary pathway thought to be responsible for the CNS signs is diffusion of lidocaine via CSF by absorption into the subarachnoid space across the dura mater from the epidural space, similar to the mechanism of sedation induced by intrathecal injection of local anesthetic agent (Pollock et al., 2000). The lidocaine concentration within the CSF when injected epidurally reaches a peak before 30 minutes and then decreases sharply (Lund and Covino, 1967), which could explain the temporary manifestation of CNS disorders. In addition, the increased frequency of symptoms in the higher volume treatments could also be explained by an increase in lidocaine concentration within the CSF. An increase in the epidural volume might result not only in a dose increase but also an increased absorption ratio into the CSF by extending the contacted surface between the distributed lidocaine and the dura mater.

The intermittent cough was suspected to be due to saliva aspiration from dysfunction of protective laryngeal reflexes. This might have resulted from incomplete block of the recurrent laryngeal nerve although there was no inspiratory stridor caused by laryngeal paralysis. Considering the anatomical location of the recurrent laryngeal nerve around vertebral columns from the C2 or C3 to T4 or T5 vertebral levels (Done et al., 2009), this nerve block may have been induced by leakage of epidural lidocaine via the intervertebral foramen. Paravertebral leakage of epidural solution around the cervicothoracic junction has been documented in human studies regarding spontaneous CSF leak syndrome and cervical

epidurography (Schievink, 2006; Emberton and Tan, 2009), and a similar leakage pattern from C6 to T2 was verified in dogs through epidurography in this study. This epidural leak pattern can potentiate the recurrent laryngeal nerve block at the vertebral level around the cervicothoracic junction. Consequently, one potential consideration is monitoring for aspiration pneumonia due to recurrent laryngeal nerve block when excessively high thoracic epidural volume results in cervicothoracic distribution, particularly in the unintubated conscious patient.

Unfortunately, cardiopulmonary monitoring during TEA was not performed in this study because it was thought that the monitoring could disrupt the SB test in conscious dogs. Furthermore, the complications were unexpected because the volumes used in this study were recommended doses for epidural catheter technique in small animal practice (Wetmore and Glowaski, 2000; Hansen, 2001). Therefore, although the CNS signs were temporary and there were no sequelae after recovery, it still leaves room for questions whether these complications should be considered when deciding on the injection volume.

Epidurography has been used as a method to predict the extent of dermatomal blockade from the distribution of CM injected into the epidural space (Yokoyama et al., 2004). However, several authors have questioned the reliability of the relationship between ED area of CM and SB area of local anesthetic analgesia (Slappendel et al., 1988; Marret et al., 2005). The ED of iohexol differed from the SB after lidocaine injection across all treatments in this study, and their correlation was not observed for all volumes injected. If an accurate evaluation for distributed area of lidocaine is possible, it may correlate to ED of CM, although there may be some differences in the distributed extent due to different viscosity of these epidural solutions (Shimizu et al., 2008). However, the area of analgesia within the ED area

of local anesthetic solution is changeable according to the type of nociceptive stimulus (Cardoso and Carvalho, 1998). As a result, it would be difficult to accurately predict the extent of epidural blockade using epidurography. Nevertheless, epidurography was useful in the analysis of the epidural hydrodynamics of a solution according to the volume injected in this study. In particular, epidurography using CT shows not only the longitudinal distribution along the epidural canal but also the transectional distribution around the spinal cord (Iseri et al., 2010; Son et al., 2014), which facilitated verification of the volume effect on bilateral ED of iohexol in this study. Because animals cannot describe their pain, pain assessments of analgesia may be relatively inaccurate compared to those of humans. Thus, epidurography in an animal study of epidural analgesia may be more useful in providing additional information to complement the analgesic results rather than for prediction of epidural blockade.

This study was designed with repeated experiments of four different volumes in each dog to exclude the influence of individual variations in epidural anatomy on TEA, and this effort resulted in prolonged insertion of the epidural catheter. The prolonged epidural catheterization could cause fibrosis surrounding the tip of the implanted catheter, affecting the ED of solution (Aldrete, 1995). Consequently, the interval between treatments was restricted to 12 hours with a total duration of 72 hours for the study. In addition, the order of treatments was established randomly to minimize any effect of lidocaine accumulation.

## **Conclusions**

The injected volume of local anesthetic solution affected the extent and homogeneity of epidural blockade and the prevalence of temporary neurologic complications during TEA in conscious dogs. Therefore, the extent of blockade and its homogeneity for adequate analgesia should be considered when choosing an injectate volume for TEA. In addition, it is necessary to monitor neurologic signs after injecting a high volume of lidocaine into the thoracic epidural space.

## **CHAPTER IV.**

# **Clinical Application of Thoracic Epidural Analgesia with Catheter in 3 Dogs**

### **Abstract**

This study was performed to evaluate the clinical applications of TEA in dogs.

The epidural catheter technique was utilized in surgical cases where intense acute postoperative pain was anticipated (extremity amputation, n = 2; thoracotomy, n = 1). Amputations were performed after diagnoses of right phalangeal apocrine carcinoma (case 1) and nonunion of a right radius fracture (case 2), while the thoracotomy was performed for left caudal lobectomy to remove pulmonary adenocarcinoma (case 3).

All dogs were treated with fluid therapy and IV premedication for sedation and analgesia. Anesthesia was induced with propofol and maintained with isoflurane in oxygen. After induction, a L7-S1 epidural catheter was inserted aseptically and the tip of the epidural catheter was advanced cranially up to the vertebral level that corresponded to the spinal nerve innervating the surgical site. Drugs (bupivacaine, or a bupivacaine-morphine combination) for neuraxial blockade were administered through the epidural catheter to provide intra- and postoperative analgesia at an injection rate of 1 ml/minute. Postoperative epidural injections were repeated every 3-12 hours for 2-3 days, and additional systemic analgesia was not required. No complications related to epidural analgesia were observed in cases 1 and 2; however,

in case 3, the patient who had a preexisting history of intervertebral disc disease (IVDD), showed paraplegia after epidural catheterization and surgery. Although the epidural catheter was removed, the dog died before recovery from the complication due to metastasis of the pulmonary tumor.

TEA provided excellent pain relief with minimal systemic effects in patient undergoing severely painful surgery. In addition, a coordinated multidisciplinary approach was required for safe and effective management without complications.

## **Introduction**

Thoracic pain management is essential because it improves respiratory function and may decrease postoperative morbidity (Licker et al., 1999; Gotoda et al., 2001). Many analgesic protocols have been proposed to control thoracic pain, but a recent meta-analysis suggested that only thoracic epidural analgesia (TEA) significantly decreased postoperative morbidity and mortality in people (Ballantyne et al., 1998). Beyond its postoperative analgesic properties, TEA also has some advantages as a component of balanced anesthesia (Meissner et al., 1997). However, its clinical use has been of concern due to an increased possibility of neurologic damage and cardiopulmonary failure when compared to lumbar EA (Visser et al., 2008). In humans, studies have focused on TEA to overcome the potential complications and to support its clinical use (Freise and Van Aken, 2011).

In small animals, the clinical use of an epidural catheter to induce TEA has been reported (Wetmore and Glowaski, 2000; Hansen, 2001), but those studies were not focused on TEA. When compared to the considerable amount of human research focused on TEA, sufficient information regarding its clinical use seems lacking in small animals. Therefore, this report aims to evaluate the clinical usefulness of TEA, as well as the considerations and complications of TEA in dogs.

## **Materials and Methods**

### **1. Patients**

Since TEA has potential complications, such as cardiopulmonary failure (Etches et al., 1989; Shuman and Peters, 1976) and neurologic damage (Giebler et al., 1997; Swalander et al., 2000), it was selectively performed in 3 dogs, which visited to the Seoul National University Veterinary Teaching Hospital from March 2013 to August 2014, undergoing severely painful surgeries (Table 6). The analgesic protocol was discussed with owners and consent was obtained for all dogs receiving TEA with a catheter.

Table 6. Summary of signalments and pre-anesthetic evaluations in 3 dogs

	Case 1	Case 2	Case 3
Breed	Cocker spaniel	Pomeranian	Shih Tzu
Age	9 years	1 year	13 years
Weight	13.4 kg	1.4 kg	5.0 kg
Disease	Phalangeal apocrine carcinoma of thoracic limb	Nonunion of radius fracture	Pulmonary adenocarcinoma of left caudal lobe
Surgery	Amputation of thoracic limb		Thoracotomy for lung lobectomy
Preexisting disease	NRF	NRF	IVDD
Physical examination	Ataxia Pain at the lesion	Ataxia Pain at the lesion	Audible crackles Cough
Blood analysis	NRF	NRF	Anemia Increased liver enzyme panel Leukocytosis
Diagnostic imaging	NRF	NRF	Adrenal gland enlargement Gallbladder sludge Hepatic echogenicity Bi-/tricuspid valvular insufficiency
ASA status	3/5	2/5	4/5

ASA, American Society of Anesthesiologists; IVDD, intervertebral disease; NRF, no remarkable finding.

## **2. Anesthetic techniques**

Preoperative radiographs of the thoracolumbar spine were taken with the dogs positioned in right lateral and dorsal recumbency. After confirming no anatomical abnormalities, placement of an epidural catheter was planned, aiming to position the tip of the catheter at the target vertebral level corresponding to the spinal segment innervating the most cranial part of the thoracic trunk involved in the surgery. The length of catheter to be threaded into the epidural canal was calculated by adding the distance between the skin above the L7-S1 space and L7-S1 epidural space for insertion, and the distance between the L7-S1 space and target vertebra where the tip of the catheter had to be positioned.

All dogs were treated with fluid and IV premedication for sedation and analgesia, and were subsequently anesthetized with propofol and isoflurane in oxygen delivered through a rebreathing circle system (Table 7). After induction of general anesthesia, the dogs were positioned in sternal recumbency. The skin above the L7-S1 space was clipped and aseptically prepared. A Tuohy needle with the bevel directed cranially was inserted at the L7-S1 space. Correct placement of the tip of the needle into the epidural space was assessed by a popping-sensation and no-resistance to injection of 0.9% saline. The epidural catheter was equipped with an imbedded coiled spring and a stylet wire to prevent collapse and kinking during advancement along the epidural canal. Using an aseptic technique, a catheter soaked with 0.9% saline was inserted into the epidural space via the Tuohy needle. The dog was then repositioned in lateral recumbency, and the catheter was advanced cranially up to the planned target level of the thoracic vertebra (Table 7). The threading process of the epidural catheter and correct placement of the catheter tip was confirmed by radiography with a C-arm imaging system (KMC-950<sup>®</sup>; COMED, Korea).

Furthermore, inadvertent insertion of the catheter into a venous sinus or intrathecal space was verified by negative withdraw of blood or CSF, respectively. After completing the installation, the catheter was fixed on the dorsal skin with sutures and a sterile drape. At the end of the procedure, the dogs were moved to the operation room and received each surgery.

Table 7. Summary of general and epidural anesthetic procedures in 3 dogs

	Case 1	Case 2	Case 3
Sedatives	Acepromazine (0.01 mg/kg IV)	Midazolam (0.20 mg/kg IV)	Midazolam (0.20 mg/kg IV)
Analgesics	Hydromorphone (0.025 mg/kg IV)	Hydromorphone (0.025 mg/kg IV)	Remifentanyl (0.1-0.4 µg/kg/minutes IV)
Induction agents	Propofol (6 mg/kg IV)	Propofol (6 mg/kg IV)	Etomidate (3 mg/kg IV)
Maintenance agents	Isoflurane	Isoflurane	Isoflurane
Monitoring items	ECG, SpO <sub>2</sub> , f <sub>R</sub> , P <sub>E</sub> 'CO <sub>2</sub> , and sAP		
Additional treatments	Cefazolin (22 mg/kg IV)	Cefazolin (22 mg/kg IV) Glycopyrrolate (5 µg /kg IV)	Atracurium (0.3 mg/kg IV) Dobutamine (5-10 µg/kg/min IV) Enrofloxacin (10 mg/kg IV)
Duration of anesthesia	1 hour	1 hour	4 hours 25 minutes
Epidural catheter diameters	19 gauge	21 gauge	19 gauge
Injection sites	T3	T3	T6
Injection volumes	0.2 ml/kg	0.2 ml/kg	0.2 ml/kg
Intra-OP analgesics	Bupivacaine	Bupivacaine	Bupivacaine
Post-OP analgesics	Day 0 Bupivacaine or Bupivacaine-morphine combination (every 2-4 hours)		Bupivacaine (every 2-4 hours)
	Day 1 Bupivacaine-morphine combination (every 7-11 hours)		Catheter removal due to paraplegia
	Day 2 Catheter removal after last injection		MRI for diagnosis
Complications	Horner's syndrome		Multiple IVDD

ECG, electrocardiogram; f<sub>R</sub>, respiratory rate; IVDD, intervertebral disc disease; MRI, magnetic resonance imaging; OP, operation; P<sub>E</sub>'CO<sub>2</sub>, end-tidal carbon dioxide tension; sBP, arterial blood pressure; SpO<sub>2</sub>, hemoglobin oxygen saturation; T, thoracic vertebra.

## Results

### 1. Case 1

A 9-year-old male neutered, Cocker Spaniel weighing 13.4 kg underwent amputation of the right thoracic limb due to phalangeal apocrine carcinoma. Pre-anesthetic physical examination revealed ataxia and pain at the lesion, and hematologic examination revealed no remarkable findings. Using the American Society of Anesthesiologists' (ASA) physical status classification system, the patient was classified as category 3 of 5.

Acepromazine (0.01 mg/kg IV), hydromorphone (0.025 mg/kg IV; Dilid®; Hana Pharm., Korea), and cefazolin (22 mg/kg IV; Cefazoline inj.; Chongkundang Pharm., Korea) were administered. Anesthesia was induced with propofol (6 mg/kg IV) and maintained with isoflurane in oxygen. ECG, SpO<sub>2</sub>, f<sub>R</sub>, P<sub>E</sub> CO<sub>2</sub>, and invasive sAP were continuously monitored during anesthesia. A 17 G Tuohy needle was inserted at the L7-S1. A 19 G epidural catheter was introduced through the needle and advanced to the epidural space of T3. A solution of bupivacaine (1 mg/kg; 0.2 ml/kg) was administered through the catheter before the start of the procedure. Hartmann's solution (10 ml/kg/hour) was administered IV. Anesthesia was uneventful and lasted 60 minutes. The right thoracic limb was excised at the level of the mid radius, and the patient normally recovered from anesthesia.

Postoperative pain was assessed during the first 12 hours and then every 2 hours by observing the dog's behavior and the response to touching the area of skin around the wound. Whenever a pain response was observed, bupivacaine (1 mg/kg; 0.2 ml/kg) or a combination of bupivacaine (0.5 mg/kg; 0.1 ml/kg) and morphine (0.1 mg/kg; 0.1 ml/kg; morphine sulfate; Hana Pharm., Korea) was administered through the epidural catheter at a rate of 1 ml/minute. Disappearance of the pain response

was observed within 10 minutes of epidural injection. In addition, the patient was calmed in sternal recumbency. The injection interval was 2-4 hours in the first day and 7-11 hours in the second day. Additional rescue analgesia was not required, and the epidural catheter was removed 30 hours after the first injection.

Miosis and protrusion of the third eyelid were observed in the right eye after extubation, suggesting Horner's syndrome. However, these symptoms disappeared after a change in epidural solution from bupivacaine to morphine-bupivacaine combination. Although a complete neurological examination could not be performed because of the residual effects of anesthesia, no other neurologic abnormalities were detected. Horner's syndrome appeared when bupivacaine was the sole analgesic agent administered, but not when a combination of bupivacaine and morphine was used. No other complications related to TEA were observed.

## 2. Case 2

A 1-year-old male neutered, Pomeranian weighing 1.4 kg underwent amputation of the right thoracic limb for nonunion of a right radius fracture. Pre-anesthetic physical examination revealed ataxia and pain at the lesion, and hematologic examination revealed no remarkable findings. ASA status of the patient was category 2 of 5.

Midazolam (0.2 mg/kg IV; Midazolam; Bugwang Pharm., Korea), cefazolin (22 mg/kg IV), and hydromorphone (0.025 mg/kg IV) were administered by IV injection. Anesthesia was induced with propofol (6 mg/kg IV) and maintained with isoflurane in oxygen. ECG, SpO<sub>2</sub>, f<sub>R</sub>, P<sub>E</sub>CO<sub>2</sub>, and sAP were continuously monitored during anesthesia. A 17 G Tuohy needle was inserted at the level of L7-S1 and the epidural space was identified. A 21 G epidural catheter was introduced through the needle and the tip of the catheter was advanced up to the level of T3. Bupivacaine (1 mg/kg; 0.2 ml/kg) was administered through the catheter before the start of the surgical procedure. Hartmann's solution (10 ml/kg/hour) was administered during the procedure. Anesthesia lasted 1 hour. One episode of bradycardia and hypotension occurred during surgery, and glycopyrrolate (5 µg /kg IV; Mobinul® 0.2 mg/ml; Myungmoon Pharm., Korea) was administered. The right thoracic limb was excised at the level of the mid radius, and the patient recovered without any special event.

Pain was assessed regularly by observing the dog's behavior and response to touching the wound. Whenever a pain response was observed, bupivacaine (1 mg/kg; 0.2 ml/kg) was epidurally administered, and the pain response disappeared within 10 minutes of epidural injection. In addition, the patient was calmed in sternal recumbency. The injection interval was 2-4 hours in the first day, 7-11 hours in the

second day, and 12 hours in the third day. Additional rescue analgesia was not required. The epidural catheter was removed 65 hours after the first injection, and there were no complications related to TEA.

### 3. Case 3

A 14-year-old male, Shih Tzu weighing 5 kg underwent a left 6th intercostal space thoracotomy to remove a  $4.6 \times 4.2 \times 3.8 \text{ cm}^3$  tumor localized in the left caudal lung lobe. The patient had a history of suspected IVDD 6 years ago, which was treated through conservative therapies. However, the client did not mention this condition during history taking. Pre-anesthetic physical examination revealed a cough, increased bronchovesicular noise, and audible crackles over the left lung field. Hematologic examination revealed a mild leukocytosis ( $17.8 \times 10^9$  cells/L; reference interval:  $5.2\text{--}17.0 \times 10^9$ /L), a mild anemia (35%; reference interval: 43.3–59.3%), and increased liver enzyme panels including alkaline phosphatase (1114 IU/L; reference interval: 8–100 IU/L) and gamma-glutamyl transferase (60 IU/L; reference interval: 0–14 IU/L). Abdominal ultrasonography revealed diffuse heterogeneous hepatic echogenicity, bilateral adrenal gland enlargement, and sludge within the gallbladder. Echocardiography revealed mitral and tricuspid valve insufficiency with mild pulmonary hypertension. Considering these pre-anesthetic evaluations, the ASA status of patient was classified category 4 of 5.

Enrofloxacin (10 mg/kg IV; Baytril<sup>®</sup>; Bayer, Korea), midazolam (0.2 mg/kg IV), remifentanyl (0.001-0.004 mg/kg/minute IV during pre- and intraoperative periods; Ultiba<sup>®</sup>; GlaxoSmithKline, Italy) were administered IV. Anesthesia was induced with etomidate (3 mg/kg IV; Lipuro<sup>®</sup>; Brawn, Korea) and maintained with isoflurane in oxygen. Atracurium (0.3 mg/kg IV; Acrium<sup>®</sup>; Myungmoon Pharm., Korea) was administered and positive pressure ventilation was used to maintain normocapnia. ECG, SpO<sub>2</sub>, f<sub>R</sub>, P<sub>E</sub> CO<sub>2</sub>, and sAP were continuously monitored during surgery. A 17 G Tuohy needle was inserted at the level of L7-S1 and the epidural space was identified. A 19 G epidural catheter was introduced through the needle and the tip of

the catheter was advanced to the level of T6. Bupivacaine (1 mg/kg; 0.2 ml/kg) was administered through the catheter before the start of the surgical procedure. Normal saline (0.45%, 2.5–10.0 ml/kg/hour) was administered IV during the procedure. Anesthesia lasted 4 hours 35 minutes. Continuous hypotension occurred, and dobutamine (0.005–0.010 mg/kg/minutes IV during surgery; Dobutamin HCl; Myungmoon Pharm., Korea) was administered during surgery. Surgery consisted of thoracotomy followed by excision of the left caudal lung lobe.

After extubation, paraplegia was observed with failure of voluntary urination. Upon confirming that the neurologic disorder did not recover for 48 hours, the epidural catheter was removed. Magnetic resonance imaging (Hitachi ARIS Vento®; Hitachi Medical Co., Japan) was performed to investigate the cause of paralysis, and spinal compression by multiple disc extrusion at intervertebral levels of T13-L1 (approximately 50%), L1-L2 (approximately 70%), L3-L4 (approximately 20-30%), and L4-L5 (approximately 40%) was confirmed. Conservative therapy was performed to manage IVDD, but the patient did not recover from the complication. The patient died 43 days after surgery due to pulmonary metastasis of the tumor which was diagnosed as adenocarcinoma.

## **Discussion**

TEA has several advantages over other analgesic protocols that do not include regional techniques, including its ability to generate effective analgesia at lower doses thereby resulting in minimal systemic effects, to decrease the incidence of cardiac arrhythmias, to increase intestinal perfusion and motility, and to allow for early extubation (Freise and Van Aken, 2011). However, these advantages were noted only when the blockade area was adequately generated.

There have been many reports regarding inadequate analgesia followed by incomplete ED (Hogan, 1999; Hansen, 2001; Yokoyama et al., 2004). These were characterized by insufficient range along the epidural canal, unilateral blockade, and/or complete deviation from the target segment. In addition, a clinical review of small animals subjected to the epidural catheter technique reported that additional analgesia or sedation was provided in 131/182 patients (72%) due to inadequate analgesia (Hansen, 2001). Concerning the inadequate epidural blockade at low volumes in chapter II, the highest volume (0.2 ml/kg) of epidural solution was chosen for the considerable extent of longitudinal spread and even distribution along the epidural canal. Consequently, no other analgesics were required in these cases, and TEA provided excellent pain relief in patient undergoing severely painful surgery.

The risk of respiratory depression (Etches et al., 1989) and hemodynamic instability (Shuman and Peters, 1976) has been documented and associated with excessive cranial distribution caused by bolus epidural injections of high volume. Concerning the potential risks of high volume injections, close monitoring was performed during the intraoperative period in all cases. There were two episodes related to cardiovascular depression, including bradycardia and hypotension, in cases 2 and 3. However, direct correlation with epidural injection was not ascertained

because other systemic anesthetics and analgesics were concurrently used, and the episodes immediately recovered after conservative therapy. In addition,  $P_E \text{CO}_2$  (reflects respiratory function) was maintained within normal range (35-45 mmHg) or under mild hypercapnia (<60 mmHg) through spontaneous respiration, except for case 3, who was administered a neuromuscular blocking agent. Although postoperative monitoring was performed only by observing the dog's behaviors, it was speculated that the vital signs were within normal ranges because they tend to improve according to recovery from general anesthesia. In addition, laryngeal paralytic symptoms were of concern in the previous chapter, but no related symptoms (aspiratory cough or stridor) were observed in these cases. Consequently, the concern regarding cardiopulmonary depression caused by TEA was not realized during intra- and postoperative periods in these cases.

Several temporary neurologic signs (Horner's syndrome and a calming effect) were observed during the postoperative period in this study. However, depression of the CNS, such as depression and stupor, were not observed. One possible explanation is the difference in the biochemical properties of the injected local anesthetic drugs. Since bupivacaine is less absorbable and has a longer onset time compared to lidocaine, the concentration of bupivacaine within the CSF may be insufficient to produce observable CNS signs. Rather, the systemic depression effect of TEA was minimal compared to IV administration, particularly in CRI of high dose analgesics. CRI is more suitable to manage severe postoperative pain compared to bolus IV administration because it maintains effective plasma concentrations required for continued pain relief. In addition, CRI at high doses tends to cause deep sedation or a plane of light anesthesia (Brosnan et al., 2009). Since drug-induced sedation can

disrupt evaluation of the CNS level, TEA could be recommended in critically ill patients with systemic depression or in patients requiring continued CNS assessment.

Unfortunately, permanent paraplegia appeared in case 3. At first, its detection was delayed due to slow recovery from general anesthesia, patient depression caused by the disease, and absence of standing effort. Considering the permanent neurologic defect and its relationship with epidural catheterization, spinal compression caused by epidural hematoma was firstly suspected (Giebler et al., 1997). However, results of magnetic resonance imaging showed unexpected multiple intervertebral disc extrusions. Although stiffening of the epidural catheter by a stylet or spring wire has been reported to increase the risk of vascular and nerve damage (Armitage, 1990), it would be difficult for a flexible epidural catheter with a ball-shaped tip to scratch the normal annulus fibrosus of intervertebral disc.

In human anesthesia, threading the epidural catheter more than a few centimeters within the epidural space is discouraged due to the risk of damaging delicate structures within the vertebral canal, and the increased risk of the catheter bending or impinging in the intervertebral foramen (Armitage, 1990). In particular, using excessive force to thread the catheter when resistance is felt is a contraindication in children who have relatively less epidural capacity (Gunter and Eng, 1992). However, these cautions are primarily directed at venous puncture and direct neural damage, but not disc extrusion caused by damage to the annulus fibrosus. In dogs, positioning the catheter tip in the desired position is typically achieved by threading it within the vertebral canal from the point of insertion, usually the L7-S1 space (Wetmore and Glowaski, 2000; Hansen, 2001). The elongated length of catheter threading on TEA would produce unavoidable resistance of various grades during immigration along the epidural canal. However, in past human and animal studies related to thoracic

epidural catheterization, there were no complications related to direct neural damage or disc extrusion by catheter threading (Giebler et al., 1997; Swalander et al., 2000).

Although the exact etiology of this complication after epidural catheterization is unknown, the most reasonable speculations for the development of multiple disc extrusions in case 3 are the use of an epidural catheter with a relatively larger diameter and spinal stenosis generated by preexisting IVDD. Although the epidural capacity of dogs may vary according to their body size, there is currently no recommendation for the selection of catheter diameter in small animals. The author established a criteria for catheter size selection by referring to the sizes used in the previous epidural studies (21 G: <5 kg, 19 G:  $\geq$ 5 kg). According to this criterion, case 3's body weight (5 kg) was on the borderline, and the use of a 19 G catheter may have been too large for the dog's epidural capacity with IVDD. Therefore, there is a strong possibility that case 3 had developed spinal stenosis as a result of the preexisting IVDD.

The resistance generated by stenosis of the epidural passage would make it impossible to thread the catheter cranially using an unwired epidural catheter without a stylet. Insertion of a catheter of relatively large diameter into an epidural canal with stenosis may cause an increase in friction force on the surface of the annulus fibrosus and an increase in EP. In a recent investigation of 937 humans with preexisting neurologic dysfunction (including spinal stenosis and lumbar disc disease) undergoing neuraxial block, 4 patients experienced new or progressive neurological deficits (Hebl et al., 2010). Due to the low incidence of newly formed neurological deficits and the fact that there was no permanent neurological damage, this report positively evaluated neuroaxial blockade in patients with neurologic dysfunction (Bajaj, 2009).

However, considering the permanent paraplegia that occurred in this case, special care should be taken when using the epidural catheterization technique in small animals with preexisting neurologic disease. In addition, the whole process of anesthesia, surgery and patient care during hospitalization should also be considered as a cause of multiple disc extrusion in dogs with history of IVDD. Especially, when the animal hospital staffs pick up a patient under general anesthesia, vertebral column can be severely flexed by the weight of dependent parts (head and pelvic limbs) of the body. Therefore, close care should be taken when patients are moved from the induction table to the surgery room, and/or from the surgery room to the recovery cage because the preexisting neurologic disease may become worse after rough care of the patient under general anesthesia.

Epidural injection through the catheter is performed by repetitive bolus injections or constant infusion (McLeod and Cumming 2004). In humans, intermittent bolus injection is preferred over constant infusion because it results in more extensive ED and less regression of SB (Wong et al. 2006). In small animals, the clinical use of bolus epidural injection was generally performed with a fixed injection interval and intermittent rescue analgesia (Wetmore and Glowaski, 2000; Hansen, 2001). In this report, a bolus injection was administered when a pain response was observed. This was used to determine the suitable injection interval to maintain adequate analgesia. An interest point is that there was a tendency for the time interval to increase as time passed, which may be related to a decrease in postoperative acute pain as time progresses. Further retrospective studies are needed to establish a recommendation for injection intervals over time.

The decision to perform TEA is based on the clinical judgement of the veterinarian, and is dependent on the veterinarian's ability to perform the procedure. In addition,

clinical use of TEA should only be applied after considering the risk-benefit balance because complications that can result in fatal neurologic disorders may occur. Therefore, a coordinated multidisciplinary approach was required for safe and effective management without complications.

## **Conclusions**

TEA provides excellent pain relief in patients undergoing severely painful surgeries with minimal systemic effects. However, fatal neurologic complications may occur in dogs with preexisting neurologic disorders. Therefore, a coordinated multidisciplinary approach was required for safe and effective management of thoracic pain, while considering the risk-benefit balance.

## GENERAL CONCLUSIONS

EA for neuraxial blockade is preferred over strong opioids to control high intensity pain in human medicine, and has been suggested as the final step for managing uncontrollable pain in the recently modified analgesic ladder (Vargas-Schaffer, 2010). In small animals, although EA is utilized in clinics, the lack of studies related to influencing factors on EA and insufficient information regarding the use of epidural catheter techniques makes its routine use difficult in veterinary medicine. Therefore, this study was performed to evaluate the factors that influence EA in dogs.

Chapter I showed the effect of ‘difference in vertebral height’ at the thoracolumbar junction in sternal recumbency’ on EA using the epidural needle technique at the L7-S1. The cranial spread of injected solution into the epidural canal of sternally recumbent dogs was not significantly influenced by difference in vertebral height at the thoracolumbar junction. The study also demonstrated that rapid spread in epidural space occurred almost immediately following injection, and that spread of radiographic contrast was maximal by 20 minutes. In addition, it was verified that the mixture of CM and MB was useful for survey of hydrodynamics in the epidural space in limited experimental populations where euthanasia can be carried out.

Chapter II evaluated the effect of ‘epidural pressure according to injection speed’ on EA using the epidural needle technique at the L7-S1. The alteration of EP caused by constant rate injection and its degree were ascertained by separating the injection and pressure monitoring lines. The peak EP was directly correlated with the injection speed of the epidural solution in dogs, but not with ED and SB. In addition, it was verified that CT provides better resolution than radiography for hydrodynamic studies of an injected epidural solution.

Chapter III concluded the ‘volume effect of local anesthetic solution’ on thoracic EA using the catheter technique. The injected volume of local anesthetic solution affected the extent and homogeneity of epidural blockade, as well as the prevalence of temporary neurologic complications. Therefore, the extent of blockade and homogeneity required for adequate analgesia should be concurrently considered when choosing an injectate volume for thoracic EA. In addition, it is necessary to monitor for neurologic signs after injecting a high volume of lidocaine into the thoracic epidural space in dogs.

Chapter IV discussed the clinical considerations regarding the use of thoracic EA using the catheter technique. EA provided excellent pain relief in patients undergoing severely painful surgeries. However, a fatal neurologic complication occurred in a dog with a preexisting neurologic disorder. Therefore, a coordinated multidisciplinary approach was required for safe and effective management of thoracic pain, while considering the risk-benefit balance.

The present study demonstrated that EA was primarily influenced by injection volume, but not by difference in vertebral height in sternal recumbency, and epidural pressure according to injection speed. In addition, the volume factor increased not only the extent of epidural blockade, but also its homogeneity. Therefore, relatively high volume of injection is recommended for even and adequate analgesia when performing EA using an epidural catheter as well as an epidural needle. The clinical use of EA with considering influencing factors provides effective analgesia without additional systemic analgesics, but a coordinated multidisciplinary approach is required to prevent the potential complications.

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# 국 문 초 록

## 개의 경막외마취에 영향을 미치는 인자의 평가

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본 연구는 개의 경막외마취에 영향을 미치는 인자를 평가하여 경막외마취에 대한 실질적인 기준을 제시하기 위해 실시하였으며, 총 4개의 장으로 구성하였다.

제1장에서는 ‘흉와위에서 흉요추 부위의 높이 차이’가 경막외마취침을 이용한 경막외마취에 미치는 영향을 검토하였다. 조영제-메틸렌블루 혼합용액을 요천추 경막외공간에 주사하고 경막외강 상행경사로 (주사위치로부터 가장 높은 척추까지)의 수직높이 및 각도에 따른 경막외분포를 평가한 결과, 경막외분포와 수직높이 및 각도와의 유의적인 연관성은 확인되지 않았다. 조영제-메틸렌블루 혼합용액은 경막외용액의 유체역학연구를 용이하게 하였으며, 요천추 부위의 높이 차이가 경막외용액의 분포에 영향을 미치지 않는다는 것을 확인하였다.

제2장에서는 ‘주사속도에 따른 경막외강압력’의 증가가 경막외마취침을 이용한 경막외마취에 미치는 영향을 검토하였다. 압력측정장비에 연결된 두 개의 척수침을 각각 제6번 및 제7번 요추사이 및 요천추 경막외공간에 삽입한 후, bupivacaine-*iohexol* 혼합용액을 요천추 부위 경막외강에 투여하는 동안 각각의 척수침을 통해 경막외강압력과 주사압력을 측정하였다. 1 및 2 ml/minute의 속도로 주사한 후, 경막외분포와 감각차단영역을 평가하였다. 주사속도에 따라 최고 경막외강압력 및 최고 주사압력에서 유의적인 차이가 확인되었으나, 경막외분포와 감각차단영역에서는 유의적인 차이가 확인되지 않았다. 주사부위와 압력측정부위를 분리하여 정확한 경막외강압력의 측정이 가능하였으며, 주사속도의 증가가 경막외강압력을 증가시키나, 경막외분포와 감각차단영역에는 영향을 미치지 않음을 확인하였다.

제3장에서는 ‘국소마취제의 투여량’이 카테터를 이용한 흉추 경막외마취에 미치는 영향을 검토하였다. 카테터를 통하여 네 가지 용량(0.05, 0.10, 0.15, 0.20 ml/kg)의 lidocaine을 제7번째 흉추 경막외공간에 투여하였다. 감각차단영역의 범위와 균질성이 투여용량에 비례하여 증가함을 확인하였다. 일부 개체에서 일시적인 신경증상(Horner 증후군, 운동실조, 후지마비, 진정, 혼미, 기침)이 관찰되었다. 이와 같은 결과들은 국소마취제의 투여량을 결정할 때, 진통영역의 범위 외에도 균질성과 합병증의 발생이 함께 고려되어야 함을 제시하였다.

제4장에서는 카테터를 이용한 흉추 경막외마취를 개에서 임상적으로 적용하여 그 유효성을 평가하였다. 우측 전지 절단술(n=2)과 폐엽절단술을 위한 개흉술(n=1)에서 bupivacaine 혹은 bupivacaine-morphine 합제를 수술 중·후 진통을 위해 반복적으로 투여하였다. 효과적인 진통과 최소의 전신 부작용을 확인하였으나, 폐엽절제술을 한 1층레에서 급성 후지마비 증상이 관찰되었으며, 자기공명 영상진단을 통해 급성 추간판탈출증이 진단되었다. 이와 같은 결과들은 경막외마취의 임상적 적용 시 합병증이 없는 안전하고 효과적인 진통관리를 위해 종합적이고 균형적인 접근이 필요함을 제시하였다.

본 연구의 결과들을 통하여, 경막외마취 시 진통발현의 범위는 주로 투여되는 약제의 부피에 의해 영향을 받으며, 흉외위에서 흉요추 부위의 높이차이와 주사속도에 따른 경막외강압력의 변화에는 영향을 받지 않음을 확인하였다. 또한 투여부피의 증가는 진통범위 외에도 진통영역의 균질성을 증가시켰다. 따라서 경막외마취 시 적절하고 고른 진통효과를 위하여 경막외마취침을 이용한 방법뿐만 아니라 카테터를 이용한 방법을 적용할 때에도 상대적으로 많은 부피로 약제를 투여하는 것이 추천된다. 그러나, 경막외마취의 적용 시에는 관련 합병증을 예방하기 위해서 종합적이고 균형적인 접근이 필요하다고 판단된다.

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주요어: 경막외마취, 영향인자, 투여용량, 경막외마취침, 경막외카테터, 개

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