การเปรียบเทียบประสิทธิภาพในการะงับปวดของทรามาดอลร่วมกับบิวพิวาเคน และมอร์ฟีน ร่วมกับบิวพิวาเคน เมื่อให้โดยวิธีการฉีดเข้าช่องเหนือเยื่อดูราในสุนัขที่เข้ารับการผ่าตัดหัวเข่า

นางสาวนถพัฒน์ บุนนาค

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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A COMPARISON OF EPIDURAL ANALGESIC EFFICACY OF TRAMADOL-BUPIVACAINE AND MORPHINE-BUPIVACAINE COMBINATIONS IN DOGS SUBJECTED TO STIFLE SURGERY

Miss Nadhapat Bunnag

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Veterinary Surgery
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Thesis Title	A COMPARISON OF EPIDURAL ANALGESIC EFFICACY OF TRAMADOL-BUPIVACAINE AND MORPHINE-BUPIVACAINE COMBINATIONS IN DOGS SUBJECTED TO STIFLE SURGERY
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นถพัฒน์ บุนนาค: การเปรียบเทียบประสิทธิภาพในการระงับปวดของทรามาดอลร่วมกับบิวพิวาเคน และมอร์ฟีนร่วมกับบิวพิวาเคน เมื่อให้โดยวิธีการฉีดเข้าช่องเหนือเยื่อดูราในสุนัขที่เข้ารับการผ่าตัดหัวเข่า. (A comparison of epidural analgesic efficacy of tramadol-bupivacaine and morphine-bupivacaine combinations in dogs subjected to stifle surgery) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผู้ช่วยศาสตราจารย์ นายสัตวแพทย์ ดร.สุมิตร ดุรงค์พงษ์ธร, 70 หน้า.

การศึกษานี้เปรียบเทียบประสิทธิภาพในการระงับปวดของทรามาดอลร่วมกับบิวพิวาเคนและมอร์ฟีนร่วมกับบิวพิวาเคน เมื่อฉีดเข้าช่องเหนือเยื่อดูราของสุนัขสุขภาพแข็งแรง 36 ตัวซึ่งเข้ารับการผ่าตัดแก้ไขสะบ้าหัวเข่าเคลื่อนระดับ 2 และ 3 สุนัขทั้งหมดได้รับการแบ่งออกเป็น 3 กลุ่มโดยการการสุ่ม (n = 12 ในแต่ละกลุ่ม) สุนัขในแต่ละกลุ่มได้รับการฉีดยาเข้าช่องเหนือเยื่อดูราดังนี้ กลุ่มควบคุม B ได้รับบิวพิวาเคนที่มีความเข้มข้นร้อยละ 0.5 ในขนาด 0.16 มล./กก.ผสมกับน้ำเกลือจนได้ปริมาตรรวม 0.2 มล./กก. กลุ่มควบคุม MB ได้รับมอร์ฟีนในขนาด 0.1 มก./กก. (มอร์ฟีน 2.5 มก./มล.) ผสมกับบิวพิวาเคนที่มีความเข้มข้นร้อยละ 0.5 เพื่อให้ได้ปริมาตรรวม 0.2 มล./กก. และกลุ่มทดลอง ได้รับทรามาดอลในขนาด 2 มก./กก. (ทรามาดอล 50 มก./มล.) ผสมกับบิวพิวาเคนที่มีความเข้มข้นร้อยละ 0.5 เพื่อให้ได้ปริมาตรรวม 0.2 มล./กก. ผลการศึกษาพบว่าระหว่างการผ่าตัดไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ ($p>0.05$) ระหว่างสุนัขกลุ่มต่างๆ ของค่าเฉลี่ยอัตราการเต้นของหัวใจ ความดันของก๊าซคาร์บอนไดออกไซด์ในลมหายใจออก ความดันของก๊าซไอโซฟลูเรนในลมหายใจออก ความดันโลหิตแดงขณะหัวใจบีบตัว และเปอร์เซ็นต์ของฮีโมโกลบินที่มีออกซิเจนจับอยู่ และค่าพารามิเตอร์ดังกล่าวมีค่าอยู่ในเกณฑ์ปกติตลอดระยะเวลาของการผ่าตัด ระยะเวลาโดยเฉลี่ยของการระงับปวดหลังผ่าตัดของสุนัขในกลุ่มควบคุม MB (21.75±0.84 ชั่วโมง) ยาวนานกว่าสุนัขในกลุ่มทดลอง TB (14±0.42 ชั่วโมง) และกลุ่มควบคุม B (6.3±0.47 ชั่วโมง) อย่างมีนัยสำคัญ สุนัขทุกตัวแสดงอาการเดินโซเซหลังผ่าตัด พบอาการน้ำลายไหลมากกว่าปกติชั่วคราวในสุนัข 1 3 และ 6 ตัว ในกลุ่มควบคุม B กลุ่มควบคุม MB และกลุ่มทดลอง TB ตามลำดับ สุนัข1 ตัวในกลุ่มควบคุม MB แสดงอาการคงค้างของปัสสาวะ จากผลการศึกษานี้สรุปว่า การให้ทรามาดอลร่วมกับบิวพิวาเคนเข้าช่องเหนือเยื่อดูราในสุนัขสามารถระงับปวดหลังผ่าตัดได้และสามารถใช้แทนมอร์ฟีนได้แต่มีระยะเวลาในการระงับปวดที่สั้นกว่า

ภาควิชา ศัลยศาสตร์..... ลายมือชื่อนิสิต..นถพัฒน์ บุนนาค.....

สาขาวิชา ศัลยศาสตร์ทางสัตวแพทย์..... ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์.....

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5175561631 : MAJOR VETERINARY SURGERY

KEYWORDS : TRAMADOL / MORPHINE / BUPIVACAINE / EPUDURAL/ DOGS

NADHAPAT BUNNAG: A COMPARISON OF EPIDURAL ANALGESIC EFFICACY OF TRAMADOL-BUPIVACAINE AND MORPHINE-BUPIVACAINE COMBINATIONS IN DOGS SUBJECTED TO STIFLE SURGERY. THESIS ADVISOR: ASST. PROF. SUMIT DURONGPONGTHORN, D.V.M., PhD, 70 pp.

This study compared the analgesic efficacy of epidural bupivacaine, the combination of bupivacaine with either tramadol or morphine in 36 healthy dogs undergoing surgical correction of patellar luxation grades 2 and 3. All dogs were randomly allocated into 3 treatment groups of 12 each and received epidural drug administration as follow. Negative control group (Group B) received 0.5% bupivacaine 0.16 ml/kg added with NSS to a total volume of 0.2 ml/kg; positive control group (Group MB) received 0.1 mg/kg morphine (morphine 2.5 mg/ml) added with 0.5% bupivacaine to a total volume of 0.2 ml/kg, and experimental group (Group TB) received 2mg/kg tramadol (tramadol 50 mg/ml) added with 0.5% bupivacaine to a total volume of 0.2 ml/kg. There were no significant differences ($p>0.05$) of average heart rate, $ETCO_2$, ET_{iso}, systolic blood pressure and SPO2 during surgery. All measured parameters were also within the normal reference ranges throughout surgery. Average duration of postoperative analgesia was significantly longer in dogs of group MB(21.75±0.84 h) than in those of groups TB(14±0.42 h) and B(6.3±0.47 h). Dogs in all groups showed sign of postoperative ataxia. The transient sign of hypersalivation was observed in 1, 3 and 6 dogs in group B, MB and TB, respectively. One dog in the MB group showed sign of urine retention. In conclusion, epidural administration of tramadol-bupivacaine provides adequate postoperative analgesia and can be used as alternative to morphine but the duration of analgesia is shorter.

Department: Veterinary Surgery..... Student's Signature Nadhapat Bunnag

Field of Study: Veterinary Surgery..... Advisor's Signature .....

Academic Year: 2010.....

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Chapter I

Introduction

Importance and Rationale.

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage and the inability to communicate in no way negates the possibility that an individual is experiencing pain or is in need of appropriate pain relieving treatment." Although acute pain serves as a protective function for animal (Muir III and Woolf, 2001) leading to disuse, rest and recuperation, guarding and avoidance, thereby minimizing further injury and promoting repair processes (Muir III, 2009a). Ongoing pain may cause many detrimental effects to the animals, for example slowing recovery, reducing food and water consumption, interfering with normal respiration, reducing a whole range of 'self – maintenance' behaviors, reducing mobility which may lead to muscle spasm (Flecknell, 2000), increasing rate of postoperative infection and sepsis, and delaying wound healing (Grant, 2006). Therefore, it is very important for us, as veterinarians, to alleviate pain in animals under our responsibilities in order to minimize unfavorable consequences associated with their ongoing pain.

All kinds of surgical procedures cause pain to the animals in varying levels depending on the severity of tissue injuries caused by each procedure. We should anticipate the levels of pain associated with surgical procedures that we will perform to our patients in order that we can choose analgesics and analgesic techniques appropriately. It has been recently accepted that, the best way in managing pain is to perform preemptive and multimodal analgesia.

Preemptive analgesia refers to the application of analgesic techniques before the patient is exposed to noxious stimuli. Examples of preemptive analgesic techniques include the use of opioids and/or alpha 2 agonists as premedicated drugs or the preoperative epidural administration of local anesthetics or opioids (Tranquilli et al., 2004). The benefits of preemptive analgesia are the ease in controlling postoperative

pain, reducing the dose of anesthetic drugs required, improving patient safety, and providing more effective pain relief (Dobromylskyj et al., 2000).

Multimodal analgesia or balanced analgesia is achieved by the simultaneous administration of two or more analgesic drug classes or techniques, in order to inhibit nociception through distinct mechanism along pain pathway (Tranquilli et al., 2004). The popularity of multimodal analgesia arises from two reasons. First, it takes advantage of additive or synergistic analgesic effects that optimize analgesia and improve patient comfort. Second, lower doses of individual analgesic agents are required, which reduces the potential for development of undesirable side effects associated with treatment (Lamont, 2008a).

Epidural analgesia, which commonly performed at the lumbosacral (L7 – Sacrum [L - S]) intervertebral space (Valverde, 2008), is an effective, safe and relatively easy procedure to perform on both dogs and cats to provide analgesia for all structures caudal to the umbilicus (Sawyer, 1998; Flaherty and MacGillivray, 2003). When administered by this route, analgesics are in close proximity to their sites of action, lower dose can be used in comparison to systemic administration resulting from the maximal binding ability of analgesics to their specific receptors (Torske and Dyson, 2000). Since lower dose can be used in providing analgesia, side effects associated with analgesics will also reduce, as they occur in dose dependent manners (Pascoe, 1997). This technique can be used as an alternative to general anesthesia or used concurrently with general anesthesia to reduce amount of anesthetic requirement during surgery (Skarda and Tranquilli, 2007). The combination of bupivacaine and morphine is widely used for epidural administration in dogs and the analgesic potency of the combination in terms of latency to effect and duration of action is known to be better than either drug administered alone with minimal side effects (Hendrix et al., 1996; Pascoe, 1997; Troncy et al., 2002; Kona – Boun et al., 2006). However, morphine is schedule II control substance in Thailand according to the narcotics act 1979, using drugs or substances in this schedule required permission from narcotic control division, careful record keeping of the purchase and dispensing, and storing in closed cabinet (Thailand Food and Drug Administration, 2003). This may make some veterinarians hesitate to use morphine for relieving pain in animals.

Tramadol is a centrally acting analgesic that is structurally related to codeine and morphine (Grond and Sablotzki, 2004). The analgesic effect of tramadol achieved from a complex interaction of at least 3 mechanism of actions (Lascelles, 2008). First, it acts as a weak opioid agonist. Second, it acts as a weak inhibitor of the reuptake of monoamine neurotransmitters (noradrenaline and serotonin) (Scott and Perry, 2000), thus activate descending inhibitory spinal monoaminergic pathways (Desmeules et al., 1996). Third, it acts as an alpha 2 adrenoceptor agonist with more binding affinity to the alpha 2A adrenoceptor than alpha 2B and alpha 2C adrenoceptors (Hocker et al., 2008). In human, it is indicated for management of moderate to moderately severe pain (Gibson, 1996; Scott and Perry, 2000; Grond and Sablotzki, 2004) with no clinically relevant effect on either respiratory or cardiovascular parameters at the recommended doses (Scott and Perry, 2000). Tramadol is never been classified as controlled substance (Hsu and Riedesel, 2008). In veterinary clinical practice, tramadol may be a useful alternative or adjunct for the treatment of acute and chronic pain (Lamont, 2008b) or cough in dogs (Plumb, 2005). The ideal analgesic should significantly reduce or eliminate post operative pain, be free of acute or chronic side effects, not be a controlled substance, and be inexpensive (Hellyer, 1997). From my point of view, tramadol meet three out of four criteria of ideal analgesics. First, it is indicated for management of moderate to moderately severe pain in human (Gibson, 1996; Scott and Perry, 2000; Grond and Sablotzki, 2004). Second, tramadol is never been classified as a controlled substance (Hsu and Riedesel, 2008). Third, it is not expensive in both oral and injectable preparations in Thailand. Although tramadol has some side effects, the side effects seem insignificant as compared with its efficacy in relieving pain.

Although epidural tramadol-bupivacaine combination (Senel et al., 2001; Majid and Mohammad, 2004; Prakash et al., 2006) have been used for postoperative pain management with success in both efficacy and long duration of analgesia, the use of tramadol by this route in animal is quite limited (Natalini and Robinson, 2000; Guedes et al., 2005). Thus, I decided to study epidural analgesic efficacy of tramadol-bupivacaine combination compared to that of morphine-bupivacaine combination administered preoperatively in dogs subjected to stifle surgery. As epidural morphine-bupivacaine combination is widely accepted in veterinary medicine that it can provide effective

analgesia with long duration for surgical procedure caudal to the diaphragm in dogs (Hendrix et al., 1996; Troncy et al., 2002; Kona-Boun et al., 2006), I decided to use this method as positive control. To my knowledge, there is no experimental clinical study on comparing the epidural analgesic efficacy of the tramadol-bupivacaine combination with that of the morphine-bupivacaine combination in dogs subjected to stifle surgery.

Objectives of Study.

To compare the epidural analgesic efficacy and side effects of the tramadol-bupivacaine combination with the morphine-bupivacaine combination administered preoperatively in dogs subjected to stifle surgery.

Research question.

Does the preoperative epidural administration of the tramadol-bupivacaine combination can provide adequate and long lasting postoperative analgesia in comparison to the morphine-bupivacaine combination in dogs subjected to stifle surgery?

Chapter II

Literature Review

Definition of Pain

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage and the inability to communicate in no way negates the possibility that an individual is experiencing pain or is in need of appropriate pain relieving treatment."

Pain pathway

Transduction : The conversion of physical stimulus into electrical activity at the peripheral nociceptor (Palmer, 2007). When the 1st order neurons, which have the naked nerve endings in the periphery with cell bodies in dorsal horn ganglia, are stimulated by noxious stimuli, they encode noxious stimuli (e.g. mechanical, chemical, or thermal stimulus) into electrical activity. The first order neurons synapse with the second order neurons located in dorsal horn (Posner, 2008).

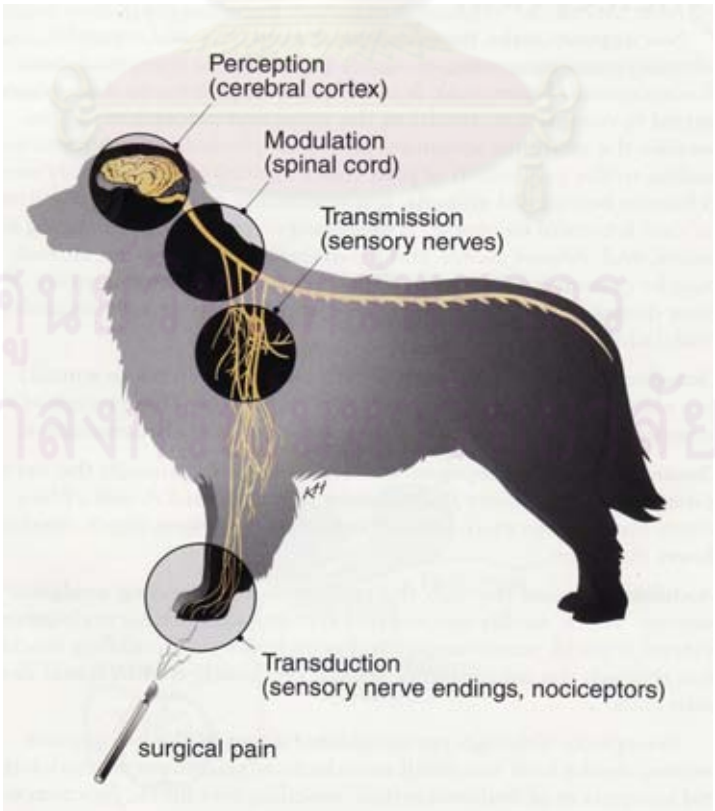


Figure 1. Physiologic processes of pain recognition (Tranquilli et al., 2004)

Transmission : The propagation of nerve impulses through the nervous system via afferent sensory fibers (Tranquilli et al., 2004). The encoded electrical activity will propagate along the afferent sensory fibers of the first order neurons to the second order neurons. Then the action potential is transmitted via ascending spinal tracts within the spinal cord. The spinothalamic tract (STT) is most prominent nociceptive pathway. The transmission of second-order neurons terminates in the thalamus (Posner, 2008).

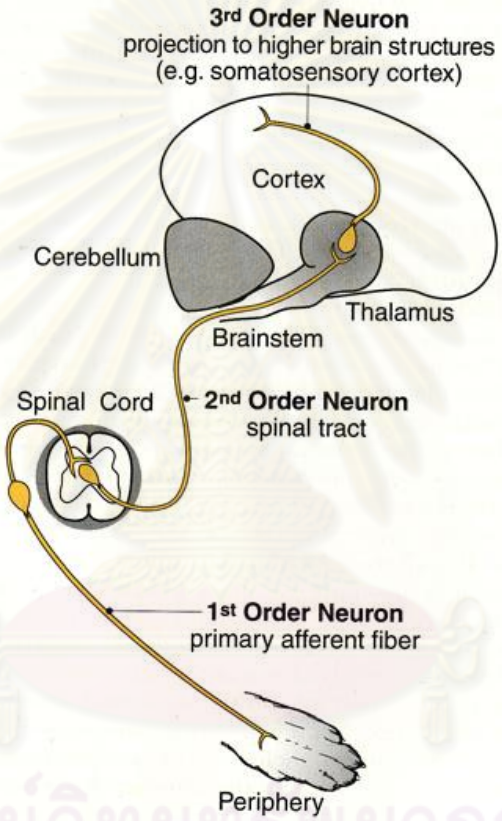


Figure 2. A simplified representation of the afferent pain pathway (Tranquilli et al., 2004)

Modulation : The process of inhibition or enhancement of signal, which occurs at the level of spinal cord (Tranquilli et al., 2004). Inhibition of signal at the dorsal horn of spinal cord can be achieved by opoids, serotonin, alpha 2 agonists, and N-methyl-d-aspartate (NMDA) antagonist (Posner, 2008).

Perception: Conscious perception of noxious stimuli is generally considered pain. Third-order neurons transmit information from the thalamus to the higher (cortical) brain centers. The cerebral cortex is considered the target for noxious stimuli. At this level the animals will perceive pain (Posner, 2008).

Pain management strategies

Preemptive analgesia refers to the application of analgesic techniques before the patient is exposed to noxious stimuli. Examples of preemptive analgesic techniques include the use of opioids and/or alpha 2 agonists as anesthetic premedication or the preoperatively epidural administration of local anesthetics or opioids (Tranquilli et al., 2004).

Multimodal analgesia or balanced analgesia is achieved by the simultaneous administration of two or more analgesic drug classes or techniques in order to inhibit nociception through distinct mechanism along pain pathway (Tranquilli et al., 2004). Drugs that can inhibit transduction are local anesthetics, opoids, and NSAIDs. Drugs that can inhibit transmission are local anesthetics and alpha 2 agonists. Drugs that act on modulation of spinal pathway are numerous for example, local anesthetics, opioids, alpha 2 agonist, NMDA antagonists, and NSAIDs. Perception can be inhibited by anesthetics, opoids, alpha 2 agonists, benzodiazepines, and phenothiazines (Lamont et al., 2000, Tranquilli et al., 2004).

The benefits of preemptive multimodal analgesia are preventing or inhibiting surgery induced peripheral sensitization and neuroplastic changes within the spinal cord, preventing the development of tachyphylaxis, suppressing the neuroendocrine stress response to pain and injury, shortening convalescence through improved tissue healing, maintaining patient immunity, improving patient mobility (Tranquilli et al., 2004), reducing the potential for development of undesirable side effects associated with treatment, and improving patient comfort (Lamont, 2008a).

Nowadays, numerous studies conducted on both dogs and humans support the advantages of preemptive (Lascelles et al., 1997; Duque et al., 2004; Altukaya et al., 2005; Karaman et al., 2006; Sibanda et al., 2006; Novello et al., 2008) and multimodal analgesia (Fowler et al., 2003; Bergmann et al., 2007; Mercadante et al., 2008; Brondani et al., 2009).

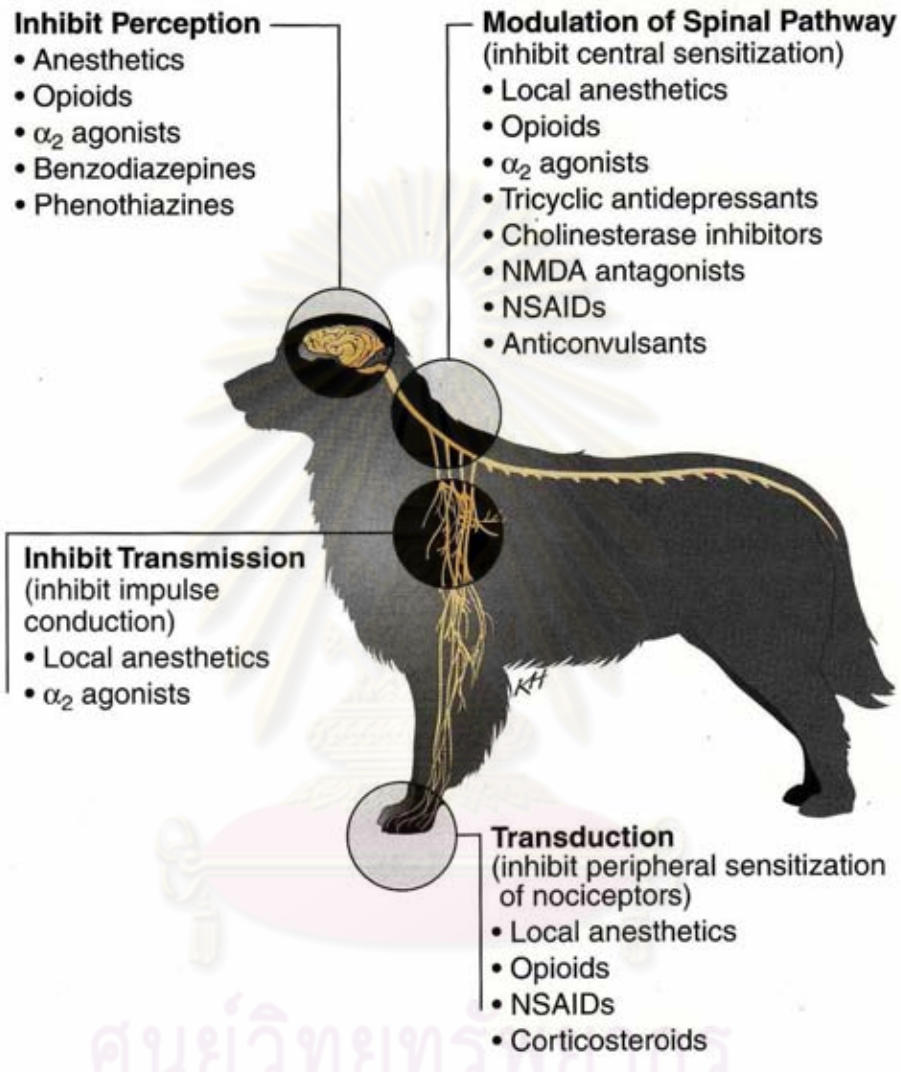


Figure 3. Pharmacologic intervention of pain processing (Tranquilli et al., 2004)

Response to pain and injury

Pain are able to induce stress response (Muir III, 2009b), by stimulating the medulla (center of circulation and ventilation), hypothalamus (center of neuroendocrine function, primarily sympathetic), and limbic structures (Hellyer et al., 2007a). The characteristics of stress response include dramatic alterations in cardiovascular, endocrine and metabolic systems (Grant, 2006). These stress responses cause elevations of blood glucose, free fatty acids, blood lactate and ketone, metabolic rate and oxygen consumption, finally leading to a catabolic state and negative nitrogen balance (Hellyer et al., 2007a).

The stress responses induced by pain are beneficial for short-term survival of organism, but can be deleterious if prolong (Hellyer et al., 2007a). Unrelieved or prolonged pain is capable in promoting an extended and destructive stress response, leading to neuroendocrine dysregulation, fatique, dysphoria, myalgia, abnormal behavior, and physical performance alteration (Muir III, 2009b).

Apart from pain, various factors can induce stress responses, for example infection, hemorrhage, heat loss, starvation, anxiety, hypoxia and acid-base changes, and tissue damage (Grant, 2006). We should do as best as we can to limit factors that induce stress responses in animals, in order to provide good quality of life for animals in our responsibilities. Many things should be done to minimize stress responses encountered by our surgical patients, for example providing adequate premedication to reduce anxiety, providing smooth induction of anesthesia to avoid dramatically release of catecholamine and cortisol, providing sufficient depth of anesthesia to counter surgical trauma and anesthetic stress (Kona-Boun et al., 2005), providing soft padded bedding for animal comfort, providing blanket to facilitate recovery from anesthesia, separating dogs from cats and decreasing visual and auditory stimulation to limit anxiety, and performing gentle and respectful handling (Hellyer et al., 2007b).

The overall detrimental physiologic effects associated with unrelieved acute pain, such as postoperative pain, are summarized in table 1.

Table 1. The detrimental effect of unrelieved pain (Grant, 2006).

Body system	Pain associated change	Consequences
Cardiovascular	Increased heart rate	Impaired cardiovascular function
	Increased blood pressure	
	Increased cardiac output	
	Increased risk of arrhythmias	
Respiratory	Increased respiratory rate	Hypoxaemia
	Reduced ventilation	Hypercapnia
		Acidosis
		Increased risk of atelectasis
		Increased risk of pneumonia
Gastrointestinal	Increased intestinal secretions	Vomiting
	Paralytic ileus	Anorexia
		Increased risk of gastric ulceration
		Intestinal pain
Urinary	Urine retention	Electrolyte changes
	Water and sodium retention	
Metabolism	Increased metabolism and	Delayed wound healing
	oxygen consumption	Increased tissue breakdown
	Breakdown of muscle, fat and	Weight loss
	glucose stores	
Immune	Impaired immune system	Increased risk of infection and
		sepsis
		Enhanced metabolic tumor spread
		Increased risk of tumor recurrence
Nervous	Sensitisation of pain pathway	Hyperalgesia and allodynia
		Heightened pain perception and
		chronic pain

Pain assessment tools in veterinary medicine

Objective Measures

Physiological variable and plasma cortisol level. Both physiological parameters (heart rate, respiratory rate, pupil size) and plasma cortisol level are the least useful in assessing pain in dogs, because they can be affected by many factors other than pain (Weary et al., 2006; Hellyer et al., 2007a). Some researchers found that heart rate, respiratory rate, and pupil size were not useful indicators of pain in hospitalized dogs following surgery (Holton et al., 1998). However, physiological parameters are useful in assessing responses to noxious stimuli in patients under general anesthesia or for transient periods in conscious patients (Mich and Hellyer, 2009).

Mechanical nociceptive threshold testing. It is used to evaluate both primary (wound) and secondary (remote area) hyperalgesia in dogs and cats (Hellyer et al., 2007a). It seems to be accurate in measuring the severity of pain, but still varies depending on age, breed (Conzemius et al., 1997; Bufalari et al., 2007), and fear of the animals (Conzemius et al., 1997).

Force plate gait analysis. It has been widely used in assessing lameness in dog, evaluating response to different surgical procedures, and assessing analgesic efficacy (Hellyer et al., 2007a; Quinn et al., 2007; Waxman et al., 2008).

Pain scoring in dogs

Pain scales that are used in veterinary medicine are adapted or modeled from those used for measuring pain in humans and primarily designed for acute pain assessment. They are mainly based on the observer's ability to assess patient's spontaneous behavior, and may incorporate other factors such as behaviors on handling, interaction with observer, reaction when injured area is manipulated by the observer, and some physiological measures (Grant, 2006). Without strictly defined criteria and the use by experienced and well-trained observers, numerous scoring systems are too variable and very subjective (Hellyer et al., 2007a).

Simple descriptive scale (SDS). It is the most basic pain scale, which usually has four or five descriptors (such as no pain, mild pain, moderate pain, severe pain, or very severe pain) for the observers to choose in assessing pain (Hellyer et al., 2007a). It is easy to use in practice but is very subjective and quite insensitive in detecting small changes or differences in pain (Grant, 2006).

Numerical rating scale (NRS). It is essentially the same as simple descriptive scale, but assign numbers for ease of tabulation and analyses; for example, absence of pain is assigned the number 0 and very severe pain the number 5 (Hellyer et al., 2007a). It is not sensitive in distinguishing subtle changes in pain (Hardie et al., 1997; Pacharinsak et al., 2003).

Categorized numerical rating system. (Table 2) A further development of the simple descriptive and numerical rating scales, where certain behaviors are chosen then assigned a value. For example, vocalization can be divided into none (score=0), crying but responsive (score=1) and crying but not responsive (score=2); other categories may include movement, agitation and posture (Hellyer et al., 2007a).

Table 2. Example of categorized numerical rating system (Conzemius et al., 1997).

Observation	Score	Criteria
Vocalization	0	No vocalization
	1	Vocalizing, responds to calm voice and stroking
	2	Vocalizing, does not respond to calm voice and stroking
Movement	0	None
	1	Frequent position changes
	2	Thrashing
Agitation	0	Asleep or calm
	1	Mild agitation
	2	Moderate agitation
	3	Severe agitation

Visual analogue scale (VAS). It consists of a continuous line (usually 100 mm long) anchored at either end with a description of the limits of the scale, for example no pain or no sedation at one end and severe pain or asleep at the other end. An observer places a mark on the line at the point that he/she thinks approximates with the degree of pain in the animal under observation, and this point is then translated into a number by measuring the distance to the mark from zero (Hellyer et al., 2007a). The VAS seems to be quite sensitive and allow for much better gradation of pain severity than the SDS, but still very subjective and required experienced person to perform assessment (Grant, 2006). It appears to be a good tool for measuring severity of pain on the condition that factors such as anxiety and delirius are identified and controlled (Conzemius et al., 1997).

Dynamic and interactive visual analogue scale (DIVAS). This is an extension of the classic VAS system in dogs. With the DIVAS system, animals are first observed from a distance undisturbed and then approached, handled and encouraged to walk. Finally, the surgical incision and surround area are palpated, and a final overall assessment of sedation and pain is made (Hellyer et al., 2007a).

Variable rating scale (VRS). (Table 3) It incorporates objective physiological data (heart rate, respiratory rate, pupil size, rectal temperature) and animal behaviors (spontaneous behaviors, posture, interactive behaviors, responses to palpation, mental status and vocalization). The observer assigns a number from the scale to each patient variable according to the definitions (or descriptors) provided. It seems to be quite sensitive and reliable between different assessors (Grant, 2006).

Table 3. Example of a VRS used in dogs (Grisneaux et al., 1999).

Variable	Criteria	Score
Heart rate	0-10% greater than preoperative value	0
	11-30% greater than preoperative value	1
	31-50% greater than preoperative value	2
	>50% greater than preoperative value	3
Respiratory rate	Normal	0
	Mild abdominal assistance	1
	Marked abdominal assistance	2
Vocalization	No crying	0
	Crying, responsive to calm voice	1
	Crying, does not responsive to calm voice	2
Agitation	Asleep or calm	0
	Mild agitation	1
	Moderate agitation	2
	Severe agitation	3
Response to manipulation	No response	0
	Minimal response, tries to move away	1
	Turns head towards site, slight vocalization	2
	Turns head with intention to bite, howls	3

The University of Melbourne pain scale. (Table 4) It is modeled on pain scale that is used to assess acute postoperative pain in children, namely Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). The University of Melbourne pain scale includes six categories. Each category contains descriptors of various behaviors that are assigned numeric values. The assessor examines the descriptors in each category and decides whether a descriptor approximates the dog's behavior. If so, the value of that descriptor is added to the patient's pain score. For mental status, the assessor must have completed a preprocedural assessment of the dog's dominant/aggressive behavior to establish the base line score. The mental status score is the absolute

difference between preprocedural and postprocedural scores. The minimum possible total pain score is 0 points; the maximum possible pain score is 27 points (Firth and Haldane, 1999). This scale has been tested on dogs following ovariohysterectomy and demonstrated good agreement between different assessors. It could also differentiate between dogs that were anesthetized but not subjected to surgery and those undergoing surgery (Hellyer et al., 2007a). The weak point of this scale is that, there is no validation of behaviors and physiologic measures used in this scale (Lascelles, 2004).

Table 4. The University of Melbourne pain scales (Firth and Haldane, 1999).

Category	Descriptor	Score
1. Physiological data		
a.	Physiologic data within reference range	0
b.	Dilated pupils	2
c. Choose only one	Percentage increase in heart rate relative to preprocedural rate	
	>20%	1
	>50%	2
	>100%	3
d. Choose only one	Percentage increase in respiratory rate relative to preprocedural rate	
	>20%	1
	>50%	2
	>100%	3
e.	Rectal temperature exceeds reference range	1
f.	Salivation	2
2. Response to palpation	No change from preprocedural behavior	0
(Choose only one)	Guards/reacts* when touched	2
	Guards/reacts* before touched	3

Category	Descriptor	Score
3. Activity	At rest: sleeping	0
(Choose only one)	At rest: semiconscious	0
	At rest: awake	1
	Eating	0
	Restless (pacing continuously, getting up and down)	2
	Rolling, thrashing	3
4. Mental status	Submissive	0
(Choose only one)	Overtly friendly	1
	Wary	2
	Aggressive	3
5. Posture		
a.	Guarding or protecting affected area (includes fetal position)	2
b. Choose only one	Lateral recumbency	0
	Sternal recumbency	1
	Sitting or standing, head up	1
	Standing, head hanging down	2
	Moving	1
	Abnormal posture (e.g., prayer position or hunched back)	2
6. Vocalization[t]	Not vocalizing when touched	0
(Choose only one)	Vocalizing when touched	2
	Intermittent vocalization	2
	Continuous vocalization	3

*Includes turning head toward affected area; biting, licking, or scratching at the wound; snapping at the handler; or tense muscle and a protective (guarding) posture.

[t] Does not include alert barking

Glasgow composite pain scale. (Table 5) To date, it is probably the most reliable and properly validated scale for assessing acute postoperative pain in dogs (Hellyer et al., 2007a; Orskov, 2010).This pain scale is modeled on the McGill pain questionnaire. The original 279 words or expressions that could describe pain in dogs have been reduced to 47 well-defined words placed in 7 categories, including posture, comfort, vocalization, attention to the wound, demeanor and response to humans, mobility, and response to touch. Each descriptor is well defined by practicing veterinary surgeons familiar with the behavioral signs of acute pain in dogs to avoid misinterpretation. Assessment involves both observation from a distance and interaction with the patient (e.g., palpation of the wound) (Holton et al., 2001).The modified form of this scale is also useful for measuring perioperative pain in clinical setting, when the assessors are not native English speakers (Murrell et al., 2008). However, this scale has some disadvantages, including lack of a numeric scoring system that would allow for comparison of scores over time, not taking into account the impact of demeanor/temperament, as well as previous experience of the patient, not accounting for residual effect of anesthetics, time consuming when use (Mich and Hellyer, 2009), and not providing the point to start analgesic intervention (Orskov, 2010).

Table 5. The Glasgow Composite Measure Pain Score (Holton et al., 2001).

The questionnaire is made up of a number of sections, each of which has several possible answers. Please check the answers that you feel are appropriate to the dog you are assessing. If more than one answer is appropriate, then check all that apply. Approach the kennel and ensure you are not wearing a laboratory coat or theater “green,” because the dog may associate these with stress and/or pain. While you approach the kennel, look at the dog’s behavior and reactions. From outside the dog’s kennel, look at the dog’s behavior and answer the following questions.
Look at the dog’s posture, Does it seem …
Rigid ( ) Neither of these ( )
Hunched or tense ( )
Does the dog seem to be …
Restless ( ) Comfortable ( )
continue

If the dog is vocalizing, Is it …

Crying or whimpering ( )
Screaming ( )
Groaning ( )
Not vocalizing/none of these ( )

If the dog is paying attention to its wound, Is it …

Chewing ( )
Ignoring its wound ( )
Licking, looking, or rubbing ( )

Now approach the kennel door and call the dog's name. Then open the door and encourage the dog to come to you. From the dog's reaction to you and behaviors when you are watching him/her, assess his/her character.

Does the dog seem to be …

Aggressive ( )
Quiet or indifferent ( )
Depressed ( )
Happy and content ( )
Disinterested ( )
Happy and bouncy ( )
Nervous, anxious, or fearful ( )

During this procedure, Did the dog seem to be …

Stiff ( )
None of these ( )
Slow or reluctant to rise or sit ( )
Assessment not carried out ( )
Lame ( )

The next procedure is to assess the dog's response to touch. If the animal has a wound, apply gentle pressure to the wound using two fingers in an area approximately 2 inches around it. If the position of the wound is such that it is impossible to touch, then apply the pressure to the closest point to the wound. If there is no wound, apply the same pressure to the stifle and surrounding area.

When touched, Did the dog …

Cry ( )
Growl or guard wound ( )
Flinch ( )
None of these ( )
Snap ( )

Continue

Definitions of expressions used in the Glasgow Composite Measure Pain Score for dogs.

Posture

Rigid: Animal lying in lateral recumbency, legs extended or partially extended in a fixed position.

Hunched: When the animal is standing, its back forms a convex shape with abdomen tucked up, or, back in a concave shape with shoulders and front legs lower than hips.

Tense: Animal appears frightened or reluctant to move; overall impression is of tight muscles. Animal can be in any body position.

Normal body posture: Animal may be in any position, appears comfortable, with muscles relaxed.

Comfort

Restless: Moving bodily position, circling, pacing, shifting body parts, unsettled.

Comfortable: Animal resting and relaxed, no avoidance or abnormal body position evident or settled, remains in same body position, at ease.

Vocalization

Crying: Extension of the whimpering noise, louder and with open mouth.

Whimpering: Often quiet, short, high-pitched sound, frequently closed mouth (whining).

Groaning: Low moaning or grunting deep sound, intermittent.

Screaming: Animal making a continual high-pitched noise, inconsolable, mouth wide open.

Attention to wound area

Chewing: Using mouth and teeth on wound area, pulling stitches.

Licking: Using tongue to stroke area of wound.

Looking: Turning head in direction of area of wound.

Rubbing: Using paw or kennel floor to stroke wound area.

Ignoring: Paying no attention to the wound area.

Demeanor

Aggressive: Mouth open or lip curled showing teeth, snaring, growling, snapping, or barking.

Depressed: Dull demeanor, not responsive, shows reluctance to interact.

Disinterested: Cannot be stimulated to wag tail or interact with observer.

Nervous: Eyes in continual movement, often head and body movement, jumpy.

Anxious: Worried expression, eyes wide with whites showing, wrinkled forehead.

Fearful: Cowering away, guarding body and head.

Quiet: Sitting or lying still, no noise, will look when spoken to but does not respond.

Indifferent: Not responsive to surroundings or observer.

Content: Interested in surroundings, has positive interaction with observer, responsive, and alert.

Bouncy: Tail wagging, jumping in kennel, often vocalizing with a happy excited noise.

Continue

Mobility

Stiff: Stilted gait, also slow to rise or sit, may be reluctant to move.

Slow to rise or sit: Slow to get up or sit down but not stilted in movement.

Reluctant to rise or sit: Needs encouragement to get up or sit down.

Lame: Irregular gait, uneven weight bearing when walking.

Normal mobility: Gets up and lies down with no alteration from normal.

Response to touch

Cry: A short vocal response. Looks at area and opens mouth, emits a brief sound.

Flinch: Painful area is quickly moved away from stimulus either before or in response to touch.

Snap: Tries to bite observer before or in response to touch.

Growl: Emits a low prolonged warning sound before or in response to touch.

Guard: Pulls painful area away from stimulus or tense local muscles in order to protect from stimulus.

None: Accepts firm pressure on wound with none of the aforementioned reactions.

Glasgow Composite Measure Pain Score-Short Form (GCMPS-SF) It is a modification of the Glasgow Composite Measure Pain Score. It is validated pain scale (Tacke, 2008), which can used as a clinical decision-making tool for assessing acute pain in dogs (Reid et al., 2007). It includes 30 descriptor options within 6 behavioral categories, including mobility. Within each category, the descriptors are ranked numerically according to their associated pain severity, and the person performing the assessment chooses the descriptor within each category that best fits the dog's behavior or condition. It is important to strictly perform the assessment procedure as described on the questionnaire (Hellyer et al., 2007a). This scale has some advantages, for example it has a numeric rating scale that facilitates therapeutic decision making and comparison among observers and over time, and the shorter format allows for easier use. However, this scale has some disadvantages, including not taking into account of demeanor/temperament, previous experience of the patient, and residual anesthetic effect (Mich and Hellyer, 2009). The pain score is the sum of the rank scores. The maximum score for the 6 categories is 24, or 20 if mobility is impossible to assess. The recommended analgesic intervention level is 6/24 or 5/20 (Reid et al., 2007). It has been used to assess pain in at least 4 researches about pain management in dogs (Carsten et al., 2008; Shih et al., 2008; Valtolina et al., 2009; Vettorato et al., 2010).

To date, there is no gold standard exists to assess pain in animals or to compare one type of scale or measurement to another (Vinuela-Fernandez et al., 2007; Mich and Hellyer, 2009), so the assessors must choose the one that most fits them and practical for use. After surgery, animals should be assessed at least hourly for the first 4-6 h, in order to be certain that the animals had fully recovered from anesthesia with stable vital sign and rested comfortably (Hellyer et al., 2007a).

Epidural drug administration

Epidural analgesia, which commonly performed at the lumbosacral [L7 – Sacrum (L - S)] intervertebral space (Otero, 2006; Valverde, 2008), is an effective, safe and relatively easy procedure to perform on both dogs and cats to provide analgesia for all structures caudal to the umbilicus (Sawyer, 1998; Flaherty and MacGillivray, 2003). When administered by this route, analgesics are in close proximity to their sites of action, lower dose can be used in comparison to systemic administration resulting from the maximal binding ability of analgesics to their specific receptors (Torske and Dyson, 2000). Since lower dose can be used in providing analgesia, side effects associate with analgesics will also reduce, as they occur in a dose dependent manner (Pascoe, 1997).

This technique is suitable for use in relieving pain for many surgical procedures, such as amputation of the tail, anal sac removal, perianal surgery, and hind limb surgeries (Flaherty and MacGillivray, 2003). In addition to relief pain associated with surgical procedures mentioned previously, it is also a useful technique for relieving pain in critical care patients, which are suffered from abdominal, hind limbs, and tail pain (Wetmore and Glowaski, 2000). This technique can be used as an alternative to general anesthesia (Cruz et al., 1997; Hewitt et al., 2007; Skarda and Tranquilli, 2007) or used concurrently with general anesthesia to reduce the amount of general anesthetic required during surgery (Cruz et al., 1997; Jones, 2001; Almeida et al., 2007; Skarda and Tranquilli, 2007). When epidural analgesia is performed before surgery, it provides not only preemptive and intraoperative analgesia with a minimum alveolar concentration reducing advantage but also excellent postoperative analgesia for long period (Valverde et al., 1989; Valverde et al., 1991; Hendrix et al., 1996; Troncy et al., 2002; Hoelzler et al., 2005; Kona – Boun et al., 2006).

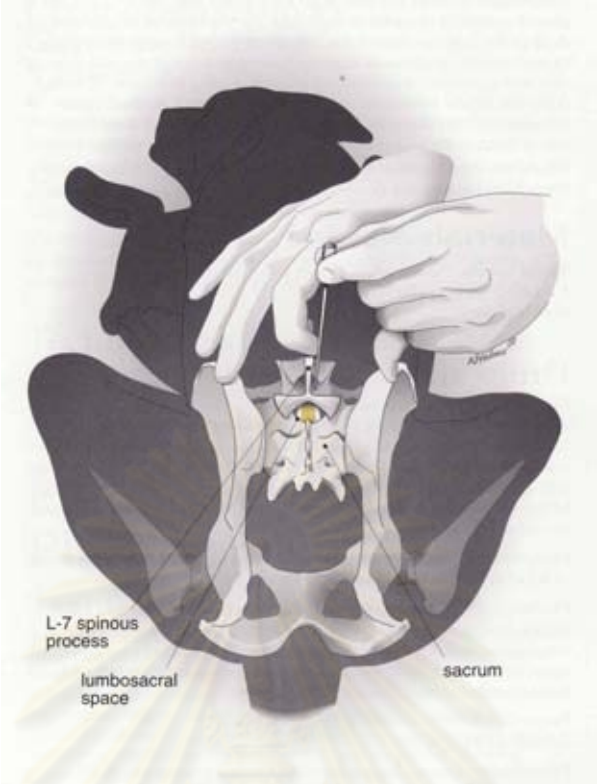


Figure 4. Anatomic landmarks for epidural technique (Tranquilli et al., 2004)

Wide variety of drugs can be used in this technique including local anesthetics (i.e., lidocaine and bupivacaine), opioids (i.e., morphine and oxymorphone), alpha 2 agonists (i.e., xylazine and medetomidine), and ketamine (Hall et al., 2001; Jones, 2001; Skarda and Tranquilli, 2007; Valverde, 2008). These drugs can be administered either alone or in combinations to achieve desirable analgesia. The most frequently used combination is the combination of a local anesthetic and an opioid, which can provide desensitization of surgical site during surgery in combination with long-term postoperative analgesia (Valverde, 2008). In addition, this combination is also an excellent mean to decrease abdominal and hind limb pain (Hellyer and Fails, 2003), particularly when pain on movement is assessed (Haetzman and Stickle, 1999).

The morphine-bupivacaine combination is widely used for epidural administration in dogs and the analgesic effect of the combination is known to be better than either drug administered alone (Hendrix et al., 1996; Pascoe, 1997; Troncy et al., 2002; Kona – Boun et al., 2006). When the combination of bupivacaine (1.5 mg/kg) and morphine (0.1 mg/kg) was administered preoperatively via extradural route in dogs

undergoing femoro-tibial joint surgery, it could reduce the neuroendocrine stress response with no effect on the inflammatory response (Sibanda et al., 2006).

Contraindications to epidural drug administration are local infection, neurologic dysfunction, obesity (difficulty in palpating landmarks), hypovolemia, hypotension (Millis, 2006), inflammation, coagulopathy, and pathology in the area of the lumbosacral junction (Grimm and Marks, 2005).

Bupivacaine

Bupivacaine (Marcaine®), a remarkably stable local anesthetic, is resistant to boiling with strong acid or alkali and shows no change on repeated autoclaving (Hall et al., 2001). It is commercially available as a 0.25%, 0.5% or 0.75% solution with or without added adrenaline (Flaherty and MacGillivray, 2003). The potency of bupivacaine is approximately four times that of lidocaine (Hall et al., 2001). It blocks nerve impulse conduction by inactivating sodium channels, thus totally disrupts neural transmission of information by axons at the treatment site and provides true analgesia (Shaffran, 2007). It also demonstrates significant separation of sensory and motor blockage, particularly when dilute solution is employed (Hall et al., 2001). At the concentration of 0.1%-0.25%, bupivacaine seems to provide analgesia with minimal motor blockade (Otero, 2006).

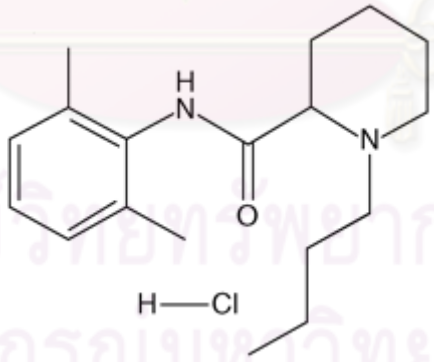


Figure 5. The chemical structure of bupivacaine (Yi et al., 2009)

Epidural bupivacaine administration can be done at dose range from 1.5 to 2.5 mg/kg (Pascoe, 1997). The duration, quality and extent of block are mostly affected by concentration (Gomez de Segura et al., 2009) and volume of bupivacaine (Freire et al., 2010). At the volume of 1 ml/5kg of body weight, the blockade can be achieved up to the level of L2 (Robertson, 2005). The onset time is about 10 – 15 min (Dobromylskyj et al., 2000) with the duration of action about 4-6 h (Grimm and Marks, 2005).

Adverse effects associated with epidural bupivacaine administration include hypoventilation secondary to respiratory muscle paralysis; hypotension, Horner's syndrome and hypoglycemia caused by sympathetic blockage; Shiff – Sherrington – like reflexes; and muscular twitches, coma, convulsion and circulatory depression caused by toxic plasma concentrations of local anesthetic (Skarda and Tranquilli, 2007), which may occur as the result of accidental overdose or inadvertent intravenous administration (Shaffran, 2007). In an attempt to prevent or treat hypotension associated with epidural bupivacaine administration, many things should be done. For example, up to 20 ml/kg of crystalloid solution is administered intravenously as a vascular preload (Jones, 2001), and an alpha-1 agonist such as phenylephrine or ephedrine can be administered to treat hypotension that not response to vascular loading (Dobromylskyj et al., 2000). The local anesthetic should be given slowly over about 30-60 seconds (Jones, 2001) with maximum volume of 6 ml (Pascoe, 1997; Wetmore and Glowaski, 2000) and the patient should be positioned with their proximal part of the body higher than the caudal part (Valverde, 2008).

Morphine

Morphine is the gold standard for pure opioid agonists. All other drugs in this class are compared to morphine in terms of efficacy, duration of action, and cost (Shaffran, 2007). It is effective for treatment of both visceral and somatic pain, particularly when medium to long term analgesia is required (Nicholson and Christie, 2002). Apart from its use as an analgesic, morphine is also an effective centrally acting antitussive in dogs (Plumb, 2005). It has been widely used in conjunction with acepromazine as premedicated drug to provide sedation and preemptive analgesia (Nicholson and Christie, 2002).

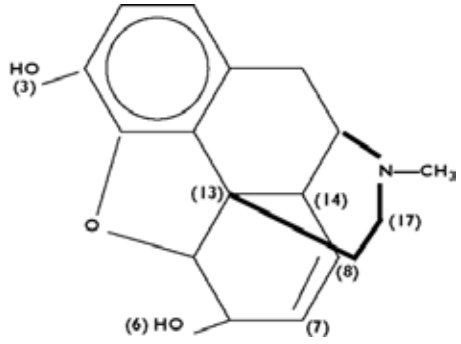


Figure 6. The chemical structure of morphine (Armstrong and Cozza, 2003)

Morphine can be administered via various different routes, namely intramuscular, intravenous (as bolus over 2-3 minutes, or continuous infusion), ocular routes (Hughes, 2008), epidural, and intra-articular (Day et al., 1995; Hughes, 2008).

Potential side effects of systemic morphine in dogs are histamine release (intravenous administration), constipation (Hellyer and Fails, 2003), sedation, dysphoria or excitement (uncommonly seen when morphine was given in painful animals), respiratory depression, bradycardia, and vomiting (Hellyer and Fails, 2003; Adamantos, 2008). The emetic effect of morphine is mediated via stimulation of chemoreceptor trigger zone (CTZ) (Takahashi et al., 2007).

Epidural morphine 0.1 mg/kg can provide analgesia for 12-24 h (Millis, 2006; Chohan, 2010) with an onset time of 30-60 min (Otero, 2006; Chohan, 2010). Although various side effects associated with epidural morphine, such as pruritus, respiratory depression, sedation, nausea or vomiting, urinary retention (Weller et al., 1991; DeConti et al., 1993; Haberkern et al., 1996), and bradycardia (Haberkern et al., 1996) are found in human, the only potential side effect associated with epidural morphine administration in dogs is delayed respiratory depression (Nicholson and Christie, 2002). Continuous epidural morphine (0.08 mg/h) demonstrates the ability to facilitate gastric emptying and intestinal transit in experimental dogs undergoing abdominal surgery, thus it may be useful in facilitating recovery from paralytic ileus after open abdominal surgery (Nakayoshi et al., 2007).

Tramadol

Tramadol is a centrally acting analgesic that is structurally related to codeine and morphine (Grond and Sablotzki, 2004). The analgesic effect of tramadol achieved from a complex interaction of at least 3 mechanism of actions (Lascelles, 2008). First, it acts as a weak opioid agonist. Second, it acts as a weak inhibitor of the reuptake of monoamine neurotransmitters (noradrenaline and serotonin) (Scott and Perry, 2000), thus activate descending inhibitory spinal monoaminergic pathways (Desmeules et al., 1996). Third, it acts as an alpha 2 adrenoceptor agonist with more binding affinity to the alpha 2A adrenoceptor than alpha 2B and alpha 2C adrenoceptors (Hocker et al., 2008). Tramadol is a racemic mixture, which both enantiomers contribute to analgesia

through different mechanism of actions. The (+) enantiomer acts as both a mu opioid agonist (Grubb, 2010a) and a serotonin reuptake inhibitor (Bamigbade et al., 1997; Grubb, 2010a). The (-) enantiomer acts as a noradrenaline reuptake inhibitor (Halfpenny et al., 1999; Grubb, 2010a). The affinity of tramadol for the μ receptor is about 6000-fold and 10-fold less than that of morphine and codeine, respectively (Miranda and Pinardi, 1998).

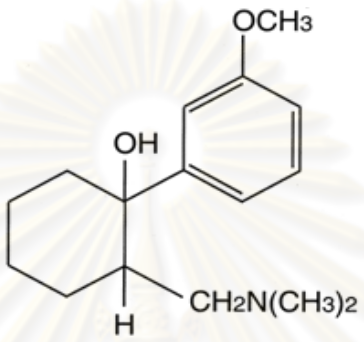


Figure 7. The chemical structure of tramadol (Hara et al., 2005)

The postoperative analgesic potency of tramadol is about 10% of that of morphine (Grond and Sablotzki, 2004) and comparable to that of pethidine following parenteral administration (Grond and Sablotzki, 2004; Slingby, 2009). When administered epidurally, tramadol is one-tenth as potent as morphine in horses (Natalini and Robinson, 2000). In children (aged 4-10 years) undergoing inguinal herniorrhaphy, preoperative epidural tramadol 2 mg/kg provided reliable postoperative analgesia similar to epidural morphine 0.03 mg/kg in both quality and duration of analgesia and could also reduce intra-operative sevoflurane requirements (Ozcengiz et al., 2001). In human, tramadol is indicated for management of moderate to moderately severe pain (Gibson, 1996; Scott and Perry, 2000; Grond and Sablotzki, 2004) with no clinically relevant effect on respiratory or cardiovascular parameters at the recommended doses (Mildh et al., 1999; Scott and Perry, 2000; Wiebalck et al., 2000). Tramadol is never been classified as controlled substance (Hsu and Riedesel, 2008). Apart from analgesic effect, tramadol also demonstrates local anesthetic effect in both experimental (Jou et al., 2003; Haeseler et al., 2006; Mert et al., 2007) and clinical studies (Altunkaya et al., 2003; Altunkaya et al., 2004; Demiraran et al., 2006; Ugur et al., 2008; Kargi et al., 2010) and antidepressant-like effect in rat (Munro et al., 2008) and mice (Jesse et al., 2010).

Additionally, tramadol shows the ability to stimulate immune system in both rats (Gaspani et al., 2002) and mice (Shirzad et al., 2009).

In veterinary clinical practice, there is considerable interest in using tramadol to manage acute perioperative and chronic pain in dogs and cats (Lamont, 2008b). Tramadol is generally recommended as part of a multimodal therapy protocol to treat chronic pain, namely osteoarthritis pain (Budsberg, 2008; Clark, 2009; Rychel, 2010), neuropathic pain (Grubb, 2010b), oncology pain (Clark, 2009; Looney, 2010), and dental pain (Woodward, 2008). The recommended doses are 3-10 mg/kg PO every 8-12 h for acute pain (Lamont, 2008b) and 1-5 mg/kg PO every 6-12 h for chronic pain (Posner, 2008).

Tramadol is metabolized in liver and excreted by kidney (Plumb, 2005; Saccomanni et al., 2010), dose should be adjusted when used in patients with renal or hepatic impairment (Plumb, 2005). Side effects of tramadol in dogs include sedation (fairly common), constipation, and seizures (uncommon and usually not require treatment) (Grubb, 2010a). As tramadol can induce seizure, it should be avoid in patient with history of seizure (Lamont, 2008b). Tramadol should not be used in patients that may have received monoamineoxidase inhibitors (MAOIs) such as selegiline (Lamont and Mathew, 2007) or tricyclic antidepressants, which also increase circulating serotonin levels. Elevated serotonin levels can lead to “serotonin syndrome,” which can be expressed as drowsiness, restlessness, altered mentation, muscle twitching, high body temperature, shivering, diarrhea, unconsciousness, and death (Posner, 2008; Grubb, 2010a).

Although the use of tramadol in veterinary medicine has gained popularity for several years, the studies about tramadol in dogs are quite limited. Some researchers conducted the study to examine pharmacokinetics of tramadol and mono-O-desmethyltramadol (M1) following intravenous and oral tramadol administration to six healthy dogs, as well as intravenous M1 to three dogs. Following 4.4 mg/kg tramadol was administered intravenously, the calculated parameters for half-life, volume of distribution, and total body clearance were 0.80±0.12 h, 3.79±0.93 L/kg, and 54.63±8.19 ml/kg/min, respectively. Following oral tramadol 11 mg/kg, the systemic availability was 65±38% and half-life of 1.71±0.12 h. The half-life of M1 following intravenous and oral

administrations of tramadol were 1.69±0.45h and 2.18±0.55 h, respectively. Following intravenous M1 administration, the half-life, volume of distribution, and clearance were 0.94±0.09 h, 2.80±0.15 L/kg, and 34.93±5.53 ml/kg/min, respectively. Simulated oral dosing regimens at 5 mg/kg every 6 h and 2.5 mg/kg every 4 h predicted tramadol and M1 plasma concentrations were consistent with analgesia in human (Kukanich and Papich, 2004). Another study on pharmacokinetics of intravenous tramadol in dogs was done by other researchers (McMillan et al., 2008). In this study, 6 healthy male mixed breed dogs were administered tramadol intravenously with three different doses (1, 2, and 4 mg/kg), the pharmacokinetics of tramadol and mono-O-desmethyltramadol (M1) and pharmacodynamic of tramadol were determined afterward. The results of this study confirmed the results of the study of Kukanich and Papich (2004) that tramadol has rapid elimination rate, high volume of distribution with high tissue affinity, high rate of clearance, and the ability of the dogs in producing M1 metabolite even with low quantity. For the results of pharmacodynamic evaluation, sedation scores increased with increasing doses of intravenous tramadol and lasted for 2 h following the administrations and there was no depression of heart rate or respiratory rate following intravenous administration of tramadol at all dosage ranges. The postoperative analgesic efficacy of preoperative intravenous tramadol 2 mg/kg and morphine 0.2 mg/kg were compared in thirty pyometra dogs undergoing ovariohysterectomy. There were no differences in analgesic efficacy, sedation, SpO_2, pH, and blood gases between dogs in tramadol and morphine groups (Mastrocinque and Fantoni, 2003). When dogs received tramadol intravenously as a loading dose of either 1.5 mg/kg followed by a continuous rate infusion (CRI) of 1.3 mg/kg/h or 3 mg/kg followed by a CRI of 2.6 mg/kg/h, both regimens revealed the ability of tramadol in reducing minimum alveolar concentration of sevoflurane (Seddighi et al., 2009). In other research, tramadol 3 mg/kg administered intravenously in experimental dogs, can increase the mechanical nociceptive thresholds with no adverse effect on renal perfusion for 24 h after normotensive anesthesia (Kongara et al., 2009).

Epidural administration of tramadol 1.0 mg/kg in 0.22 ml/kg of sterile water in ten healthy dogs undergoing stifle surgery could provide adequate postoperative analgesia for at least 4 h with no cardiovascular and respiratory depression (Guedes et al., 2005).

In other research, epidural administration of tramadol at the same dose and dilution could also provide adequate postoperative analgesia for at least 4 h with neither hemodynamic nor respiratory depression in dogs undergoing experimental excision and replacement of the cranial cruciate ligament (Natalini et al., 2007). Epidural administration of tramadol 2 mg/kg in dogs undergoing tibial plateau leveling osteotomy (TPLO) could provide satisfactory postoperative analgesia for at least 8 h without significant clinical side effects (Vettorato et al., 2010).

To my knowledge, there was no study conducted to evaluate analgesic efficacy of preoperative epidural tramadol-bupivacaine combination in dogs. However, at least four studies were done in children, to evaluate the postoperative analgesic efficacy of epidural tramadol-bupivacaine combination. The results of the studies showed that epidural tramadol added bupivacaine could provide adequate postoperative analgesia for long period of time. In first study, preoperative epidural tramadol 1.5 mg/kg with 0.25% bupivacaine 1 ml/kg provided adequate postoperative analgesia for 13.5±2.2 h, whereas epidural bupivacaine alone provided adequate postoperative analgesia for 9.8±2.0 h in children undergoing unilateral herniorrhaphy (Senel et al., 2001). In second study, preoperative epidural tramadol 1 mg/kg with 0.25% bupivacaine (0.5 ml for circumcision, 1 ml for inguinal herniotomy, and 1.25 ml for orchidopexy) in children undergoing inguinal and penoscrotal surgeries provided comparable postoperative analgesia to epidural bupivacaine alone until 6 h postoperatively, but at 8 and 12 h postoperatively, children in the combination group have significantly lower pain score than those in bupivacaine group (Majid and Mohammad, 2004). In third study, three difference doses of tramadol (1 mg/kg, 1.5 mg/kg, and 2 mg/kg) were added to 0.25% bupivacaine 0.75 ml/kg to define the most appropriate tramadol dose added to 0.25% bupivacaine. The appropriate dose of tramadol added to 0.25% bupivacaine is 2 mg/kg which could provide adequate postoperative analgesia for 12.0±0.9 h, whereas 0.25% bupivacaine 0.75 ml/kg provided adequate postoperative analgesia for 4.0±1.0 h in children undergoing inguinal herniotomy (Prakash et al., 2006). In fourth study, preoperative epidural tramadol 2 mg/kg added with 0.25% bupivacaine 1ml/kg could provide satisfactory postoperative analgesia for up to 9 h postoperatively in children

undergoing inguinal herniorrhaphy with no evidence of motor deficit (Kartalov et al., 2008).

All the results of the studies mentioned previously, showed that epidural administration of tramadol-bupivacaine combination could provide adequate postoperative analgesia without clinical significant adverse effect and dose of 2 mg/kg tramadol with 0.25% bupivacaine seems to be the most effective.

Chapter III

Materials and methods

Animals

The method of this study was approved by the Committee for the Ethical Care of Animals of the Chulalongkorn University. Informed owner consent was obtained prior to enrolment of all dogs in the study. Thirty six dogs with no breed and sex predilection, aging between 3 months and 5 years, and weighting less than 10 kg, which scheduled for surgical correction of patella luxation grade 2 or 3 at surgery unit, Small Animal Hospital, Faculty of Veterinary Science, Chulalongkorn University were enrolled in the study. Dogs were healthy according to physical examinations, complete blood counts, and blood chemistry profiles before surgeries. Dogs were randomly allocated into three treatment groups (n = 12 for each group).

Anesthesia

1. Dogs were withheld water and food for 6 and 12 h before surgeries, respectively and taken for walk to urinate and defecate before premedication.
2. Physical examination was performed and measured parameters, for example heart rate, respiratory rate, pulse quality, body temperature, hydration status, capillary refill time, mucus membrane color were recorded.
3. Acepromazine 0.03 mg/kg and tramadol 3 mg/kg were administered intramuscularly as premedication.
4. 15-30 min after premedication, an IV catheter was placed in the cephalic vein and anesthesia was induced with propofol to effect (until endotracheal intubation could be performed). Anesthesia was maintained with isoflurane in 100% oxygen delivered via a non-rebreathing anesthetic circuit. The percentage of isoflurane was adjusted to maintain a surgical plane of anesthesia as judged by eye position, jaw tone and lack of response to noxious stimuli. The respiratory rate was controlled by the ventilator at 15 breath/ minute. All dogs received crystalloid solution (Lactated Ringer

solution) intravenously at 5-10 ml/kg/h. Cefazolin (250 mg/ml) 25 mg/kg was administered intravenously as prophylactic antibiotic.

Epidural administration

The surgical site was clipped. Then dogs were positioned in sternal recumbency with both hind legs extended forward under the body. The lumbosacral space was located, hair in that area was clipped and the skin was aseptically prepared. Once dogs were at surgical plane of anesthesia, epidural drug administration was performed (as described by Jones, 2001). Dogs were randomly allocated into three groups, and received drugs as follow.

Negative control group Dogs received 0.5% bupivacaine 0.16 ml/kg added with NSS to a total volume of 0.2 ml/kg (Group B)

Positive control group Dogs received 0.1 mg/kg morphine (morphine 2.5 mg/ml) added with 0.5% bupivaciane to a total volume of 0.2 ml/kg (Group MB)

Experimental group Dogs received 2 mg/kg tramadol (tramadol 50 mg/ml) added with 0.5% bupivacaine to a total volume of 0.2 ml/kg (Group TB)

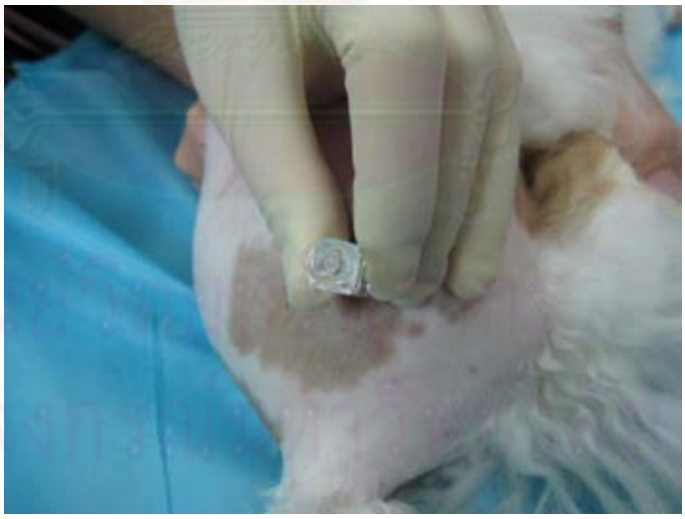


Figure 8. Lumbosacral epidural administration in dogs

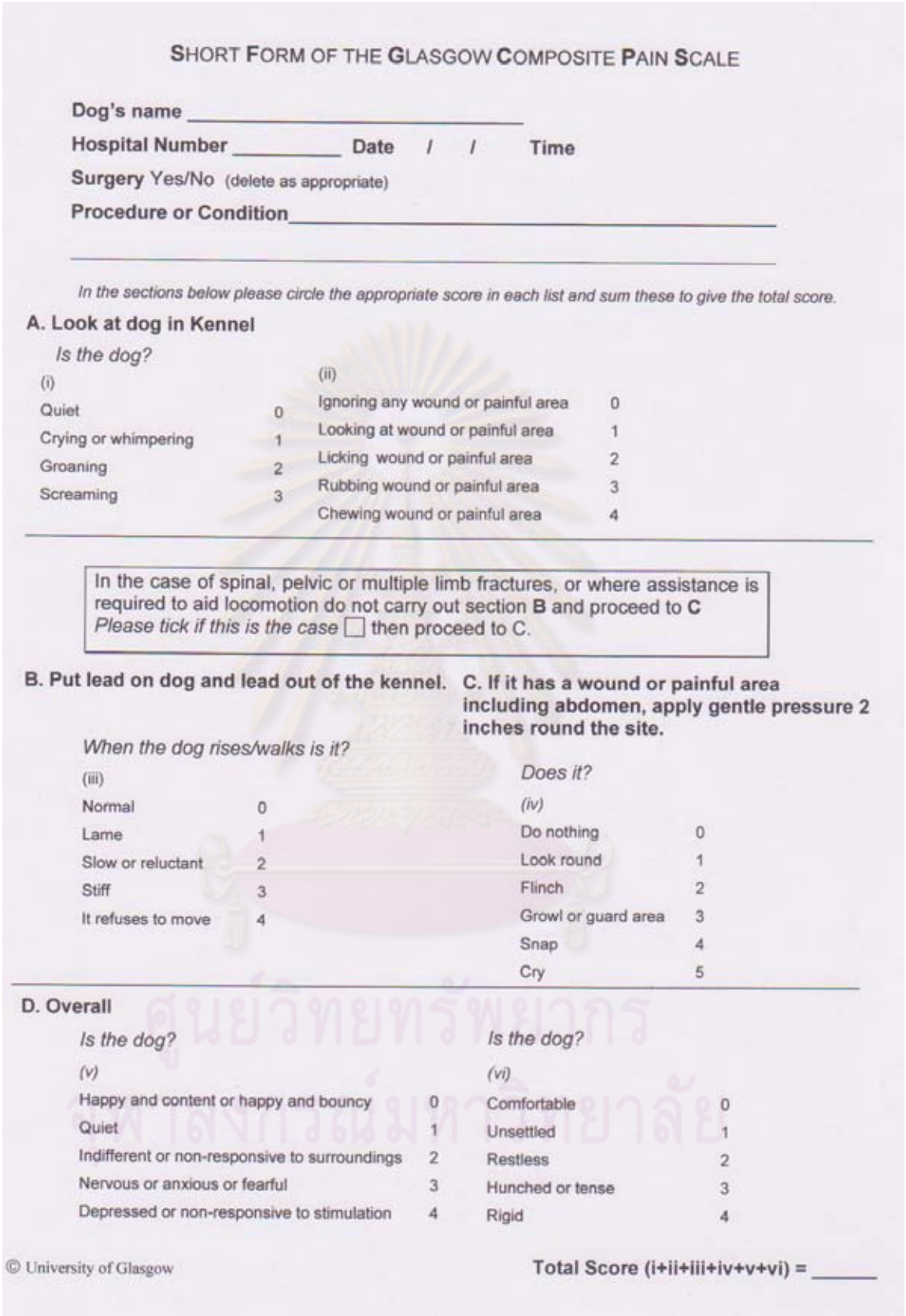
After epidural drug administration, dogs were positioned in lateral recumbency with the affected side depended for 5 min. Dogs were monitored, for side effects related to epidural local anesthetic, such as hypotension, bradycardia, and respiratory depression. When those occurred, dogs were treated appropriately.

Surgery

Surgical correction of patella luxation grade 2 or 3 was performed at least 30 min after epidural drug administration. End-tidal CO_2 (ET CO_2), end-tidal isoflurane (ETiso), heart rate (HR), noninvasive systolic blood pressure (NIBP) measured by Doppler flow detection, and oxygen saturation were recorded every 5 min until surgery was finished. Time from epidural drug administration to surgery, total surgical time, time from epidural drug administration to endotracheal extubation and total anesthetic time were recorded.

Assessment of pain and sedation

1. Pain was assessed by observer unaware of the treatment using Glasgow composite pain scale short form (GCMPS-SF) at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, 24 h postoperatively. Tramadol at 3 mg/kg was given intramuscularly at anytime point during 24 h postoperative once the pain score was over 5/20 (if mobility could not be assessed) or 6/24 and at 24 h postoperatively before returning dogs to the owners.
2. Lameness was assessed using lameness score at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, 24 h postoperatively.
3. Sedation was assessed using sedation score at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, 24 h postoperatively.
4. Side effects such as vomiting, panting, drowsiness were noted.
5. Interval between endotracheal extubation and first postoperative administration of tramadol was recorded.



SHORT FORM OF THE GLASGOW COMPOSITE PAIN SCALE

Dog's name _____

Hospital Number _____ **Date** / / **Time**

Surgery Yes/No (delete as appropriate)

Procedure or Condition_____

_____

In the sections below please circle the appropriate score in each list and sum these to give the total score.

A. Look at dog in Kennel

Is the dog?

(i)		(ii)	
Quiet	0	Ignoring any wound or painful area	0
Crying or whimpering	1	Looking at wound or painful area	1
Groaning	2	Licking wound or painful area	2
Screaming	3	Rubbing wound or painful area	3
		Chewing wound or painful area	4

In the case of spinal, pelvic or multiple limb fractures, or where assistance is required to aid locomotion do not carry out section **B** and proceed to **C**
Please tick if this is the case ☐ then proceed to C.

B. Put lead on dog and lead out of the kennel.

When the dog rises/walks is it?

(iii)	
Normal	0
Lame	1
Slow or reluctant	2
Stiff	3
It refuses to move	4

C. If it has a wound or painful area including abdomen, apply gentle pressure 2 inches round the site.

Does it?

(iv)	
Do nothing	0
Look round	1
Flinch	2
Growl or guard area	3
Snap	4
Cry	5

D. Overall

Is the dog? *(v)*		*Is the dog?* *(vi)*	
Happy and content or happy and bouncy	0	Comfortable	0
Quiet	1	Unsettled	1
Indifferent or non-responsive to surroundings	2	Restless	2
Nervous or anxious or fearful	3	Hunched or tense	3
Depressed or non-responsive to stimulation	4	Rigid	4

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Total Score (i+ii+iii+iv+v+vi) = _____

Figure 9. Short form of the Glasgow Composite Pain Scale (Faculty of Veterinary Science, University of Glasgow)

Lameness score (Duque et al., 2004)

Position	Score
Complete weight bearing	0
Partial weight bearing (standing and walking)	1
Partial weight bearing (standing only)	2
No weight bearing	3

Sedation scores (Duque et al., 2004)

Behavior	Score
Alert and walking normally	0
Somnolence, remains standing with head down and eyes semiclosed	1
Somnolence, remains in lateral or sternal recumbency, responds to calling	2
Somnolence, remains in lateral or sternal recumbency, does not respond to calling	3

Statistical analysis

Elapsed time between epidural drug administration and surgery, total surgical time, elapsed time between epidural drug administration and endotracheal extubation, and total anesthetic time were analyzed using ANOVA.

End-tidal CO_2 (ET CO_2), end-tidal isoflurane (ETiso), heart rate (HR), noninvasive systolic blood pressure (NIBP), and oxygen saturation were analyzed using analysis of variance (ANOVA).

Duration of postoperative sedation, duration of postoperative motor deficit, and interval between epidural drug administration and first postoperative administration of tramadol were analyzed using ANOVA.

Chapter IV

Results

Animals

Thirty six dogs enrolled in this study were healthy according to physical examination, complete blood count and blood chemistry profiles before surgery. Group TB consisted of 7 Pomeranians, 2 Poodles and 3 Chihuahuas. Group MB consisted of 9 Pomeranians, 2 Poodles and 1 Chihuahua. Group B consisted of 7 Pomeranians, 1 Poodle, 1 Chihuahua, 1 Miniature Pincher, and 2 Yorkshire Terriers. The proportion of male:female was 5:7, 6:6, and 5:7 in groups TB, MB, and B, respectively. There was no difference in weight among groups. Average weight (mean±SE) was 2.66±0.35 kg, 3.79±0.41 kg, and 3.32±0.57 kg in groups TB, MB, and B, respectively.

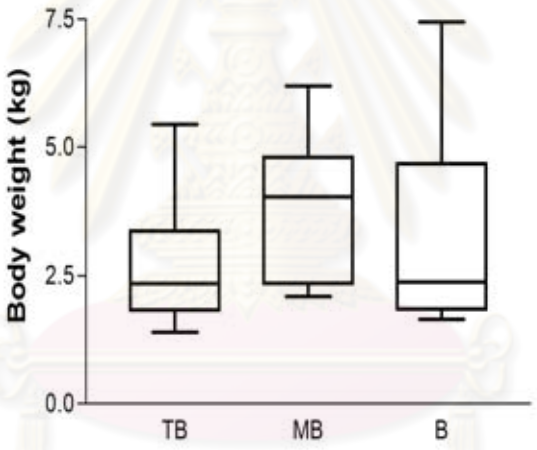

Figure 10. Average weights (mean±SE) in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Whereas, the average age in group TB was significantly younger than group MB with no significant between groups TB and B. No significant difference was detected between groups MB and B. Average age (mean±SE) was 12.5±2.51, 35.66±5.85, and 29.16±5.7 months in groups TB, MB, and B, respectively.

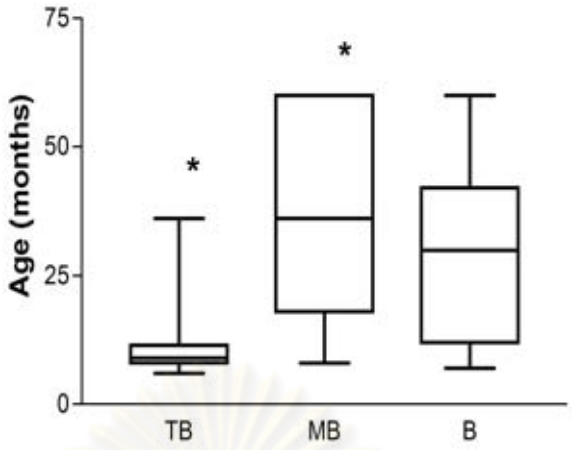

Figure 11. Average ages (mean±SE) in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

* Average ages in group TB was significantly younger than group MB

Surgical and anesthetic time

Average elapsed time between epidural administration and surgery (mean±SE) was 35.00±1.50, 35.41±1.99, and 34.58±1.78 min in groups TB, MB, and B, respectively, with no statistical differences among groups.

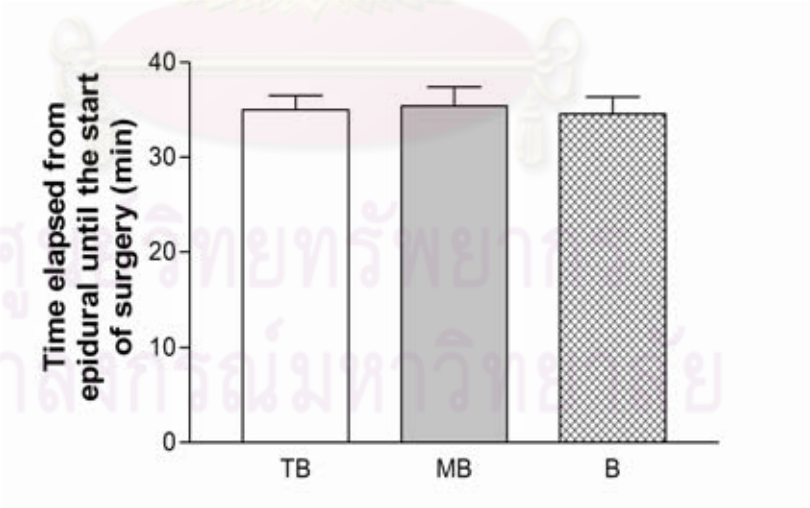

Figure 12. Average elapsed time between epidural administration and surgery in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Surgical time (mean±SE) was 45.00±3.94, 58.75±3.02, and 41.25±2.31 min in groups TB, MB, and B, respectively.

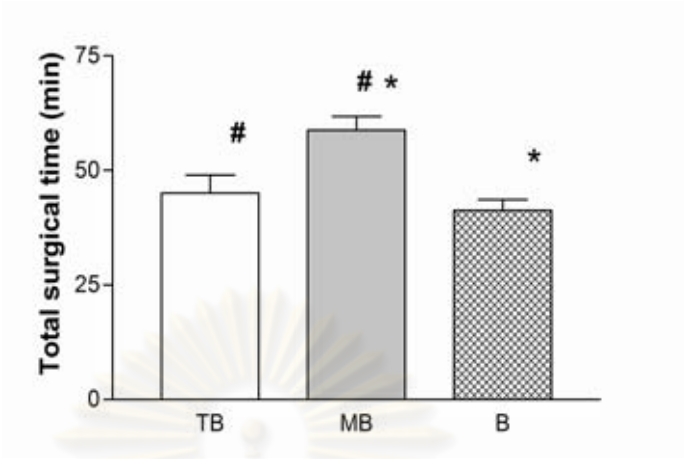

Figure 13. Average surgical time (mean±SE) in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Average surgical time in groups MB was significantly longer than group TB

* Average surgical time in group MB was significantly longer than group B

Anesthetic time (mean±SE) was 104.16±3.83, 115.41±2.25, and 102.50±3.76 min in groups TB, MB, and B, respectively.

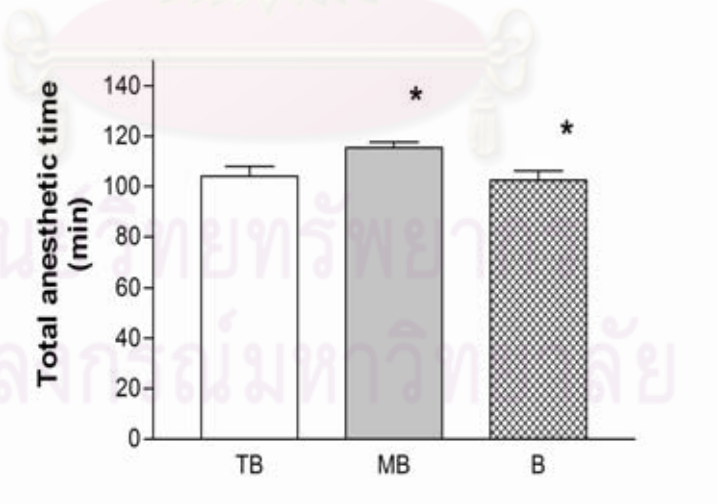

Figure 14. Average anesthetic time (mean±SE) in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

* Average anesthetic time in group MB was significantly longer than Group B

Elapsed time between epidural administration and endotracheal extubation (mean±SE) was 90.83±4.21, 103.75±2.76, and 87.50±4.19 min in groups TB, MB, and B, respectively.

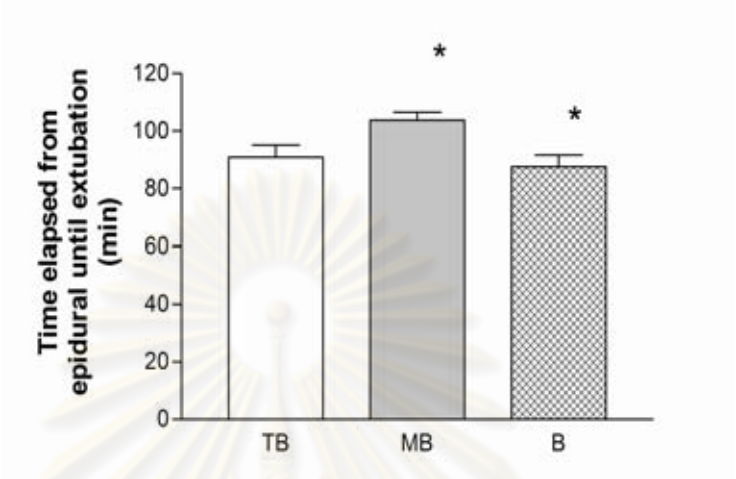

Figure 15. Average elapsed time between epidural administration and extubation in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)
* Average elapsed time between epidural administration and extubation in group MB was significantly longer than B

Surgical time was significantly longer in group MB than groups TB and B with on significant difference between groups TB and B.

Elapsed time between epidural administration and endotracheal extubation, and anesthetic time were significantly longer in group MB than in Group B, but no significant differences were observed between groups TB and B or groups MB and TB.

Measured parameters during surgery

During surgery, measured parameters namely heart rate (Table 6), oxygen saturation (Table 7), systolic blood pressure (Table 8), end-tidal carbon dioxide (Table 9), and end-tidal isoflurane (Table 10) were within normal reference levels with no statistically significant differences among groups.

Tabel 6. Average heart rate (mean±SE) during surgery in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Time(min)	Group TB (beat/min)	Group MB (beat/min)	Group B (beat/min)
0	97.17±7.99	98.58±4.47	106.67±5.65
5	98.50±6.89	103.50±5.71	107.58±6.33
10	103.33±7.59	99.67±5.02	110.33±7.92
15	96.50±6.21	102.41±5.28	107.83±7.33
20	98.75±6.44	104.08±4.38	104.25±5.75
25	97.92±6.06	97.33±4.53	105.33±6.65
30	100.27±6.23	99.25±4.29	104.70±6.22
35	99.70±7.04	99.00±4.96	111.00±7.60
40	96.67±6.76	95.50±4.56	89.00±4.14
45	87.17±2.89	91.50±4.31	109.00±17.08
50	92.50±6.24	93.90±4.48	143.00±0.00
55	91.67±9.28	93.57±6.44	-
60	96.50±16.50	92.00±4.79	-
65	94.00±0.00	102.17±9.76	-
70	96.00±0.00	97.50±10.30	-
75	96.00±0.00	-	-

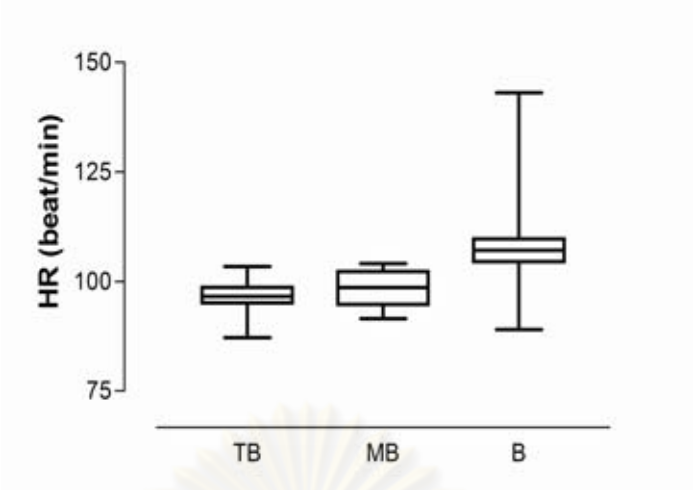

Figure 16. Average heart rate in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Table 7. Oxygen saturation (mean±SE) during surgery in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Time (min)	Group TB (%)	Group MB (%)	Group B (%)
0	96.08±0.48	97.83±0.58	98.00±0.63
5	97.50±0.60	98.08±0.54	97.50±0.58
10	97.33±0.64	98.25±0.43	97.83±0.55
15	97.92±0.46	98.25±0.51	97.83±0.52
20	97.83±0.46	98.33±0.40	98.08±0.45
25	97.83±0.42	98.17±0.41	98.17±0.39
30	98.00±0.50	98.17±0.42	98.25±0.43
35	97.10±0.48	98.25±0.30	98.40±0.31
40	97.56±0.56	97.83±0.39	97.38±0.59
45	97.50±0.62	98.08±0.45	96.40±0.60
50	95.75±0.48	98.10±0.35	96.67±0.52
55	96.67±0.33	98.43±0.61	98.32±0.32
60	96.50±0.50	98.83±0.54	-
65	97.00±0.00	98.33±0.80	-
70	97.00±0.00	98.50±0.96	-
75	97.00±0.00	-	-

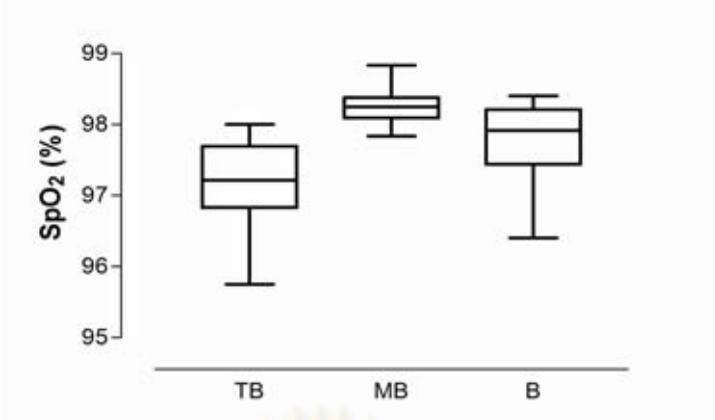

Figure 17. Average oxygen saturation in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Table 8. Systolic blood pressure (mean±SE) during surgery in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Time (min)	Group TB (mmHg)	Group MB (mmHg)	Group B (mmHg)
0	107.50±5.78	93.33±3.55	108.50±4.29
5	110.33±6.99	92.67±4.06	116.58±4.61
10	108.25±5.57	103.33±6.67	112.92±4.81
15	111.50±6.52	99.50±10.07	110.25±4.41
20	110.83±6.33	108.17±5.46	112.75±4.01
25	118.33±6.55	109.67±4.75	108.67±4.86
30	116.55±7.09	114.33±4.94	107.33±4.43
35	117.00±9.20	114.67±5.24	108.6±4.34
40	117.78±10.51	113.00±4.26	111.00±4.80
45	125.00±13.95	106.17±4.39	99.60±4.87
50	119.50±10.81	106.20±5.25	92.67±2.27
55	109.33±14.85	116.86±6.93	98.00±0.00
60	109.00±0.00	113.67±8.25	-
65	140.00±0.00	113.33±6.15	-
70	130.00±0.00	105.00±6.46	-
75	126.00±0.00	-	-

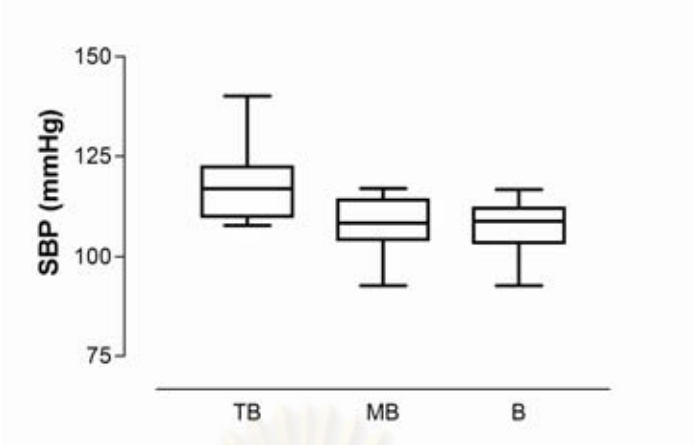

Figure 18. Average systolic blood pressure in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Table 9. End-tidal carbon dioxide (mean±SE) during surgery in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Time (min)	Group TB (mmHg)	Group MB (mmHg)	Group B (mmHg)
0	29.75±1.78	27.75±1.72	28.83±1.25
5	29.17±1.69	27.33±2.16	29.00±1.53
10	29.58±2.08	27.67±2.11	29.08±1.45
15	29.92±2.26	26.00±1.86	28.75±1.51
20	31.08±2.47	28.67±1.63	27.58±1.85
25	30.08±2.19	26.67±1.64	27.33±1.64
30	28.45±2.25	27.08±1.71	26.75±1.60
35	29.00±2.94	29.00±1.76	26.20±1.08
40	28.44±2.58	27.58±1.46	26.87±1.49
45	31.00±3.11	28.75±1.73	24.00±2.35
50	34.50±3.97	29.70±2.05	24.67±2.96
55	31.33±4.67	32.14±2.68	23.00±0.00
60	36.00±10.00	30.50±3.07	-
65	25.00±0.00	32.83±3.18	-
70	26.00±0.00	32.50±3.59	-
75	25.00±0.00	-	-

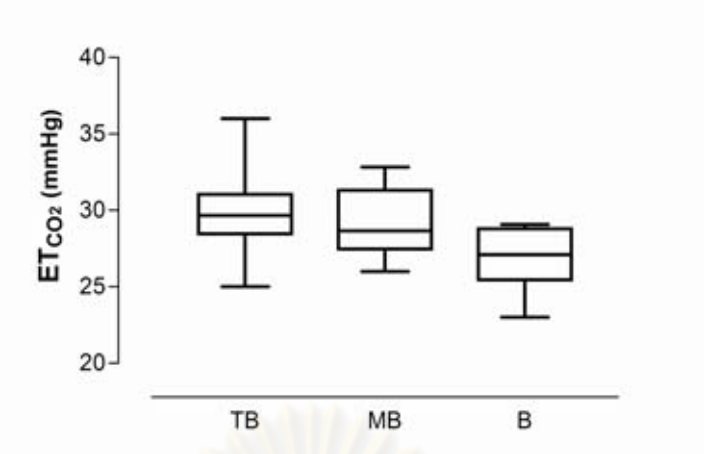

Figure 19. Average end-tidal carbon dioxide in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Table 10. End-tidal isoflurane (mean±SE) during surgery in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Time (min)	Group TB (%)	Group MB (%)	Group B (%)
0	0.86±0.11	1.07±0.07	0.77±0.07
5	0.87±0.11	0.98±0.07	0.84±0.08
10	0.89±0.07	0.89±0.07	0.78±0.08
15	0.80±0.07	0.87±0.07	0.77±0.06
20	0.76±0.10	0.89±0.06	0.90±0.09
25	0.66±0.06	0.88±0.06	0.72±0.07
30	0.68±0.07	0.85±0.06	0.69±0.08
35	0.64±0.09	0.85±0.05	0.63±0.09
40	0.65±0.08	0.82±0.05	0.56±0.11
45	0.61±0.11	0.78±0.06	0.49±0.07
50	0.71±0.14	0.73±0.07	0.46±0.02
55	0.68±0.15	0.73±0.08	0.53±0.00
60	0.62±0.25	0.74±0.11	-
65	0.44±0.00	0.71±0.10	-
70	0.43±0.00	0.66±0.15	-
75	0.43±0.00	-	-

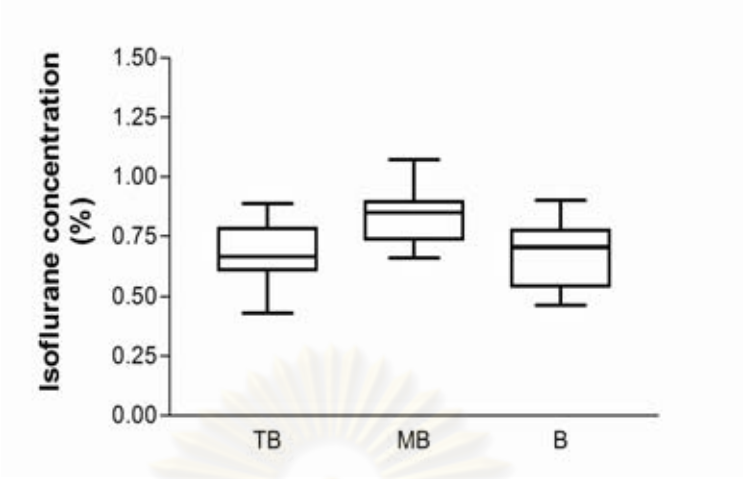

Figure 20. Average end-tidal isoflurane in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Duration of postoperative motor deficit

Duration of postoperative motor deficit in this study was judged by observing the dogs since they recovered from anesthesia until they could stand on their pelvic limbs. Duration of postoperative motor deficit (mean±SE) was significantly longer in group MB (4.75±0.89 h) than in groups TB (2.75±0.52 h) and B (2.25±0.03 h) with no difference between groups TB and B.

Duration of postoperative sedation

Duration of postoperative sedation in this study was judged by observing the dogs since they recovered from anesthesia until they show no signs of sedation. The sedation score used in this study was derived from those used in the study of Duque and others in 2004. Duration of postoperative sedation (mean±SE) was 4.00±0.40 h, 4.33±0.74 h, and 3.75±0.48 h in groups TB, MB, and B, respectively with no significant differences among groups.

Postoperative lameness

Dogs in all groups had lameness score at 3 according to no weight bearing of the affected limb throughout 24 h postoperatively.

Postoperative analgesia

Average elapsed time between endotracheal extubation and first tramadol administration (mean±SE) was significantly longer in group MB (21.75±0.84 h) than in groups TB (14.00±0.42 h) and B (6.3±0.47 h).

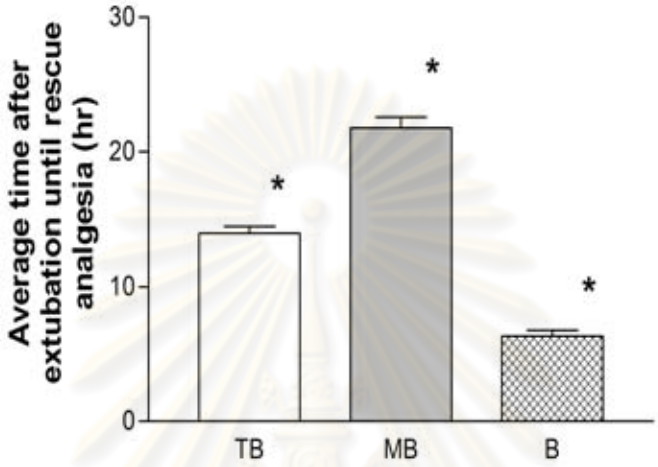

Figure 21. Average time after extubation until rescue analgesia in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)
* Average time after extubation until rescue analgesia in group MB was significantly longer than groups TB and B, respectively

Adverse effects

No adverse effects related to epidural anesthetic administration were detected either after administration or during surgery.

Hypersalivation was observed in 1(8.3%), 3 (25%), and 6 (50%) dogs in groups B, MB, and TB, respectively.

Urine retention was observed in 1 (8.3%) dog in group MB.

Table 11. Elapsed time between epidural administration and surgery, surgical time, elapsed time between epidural administration and extubation, anesthetic time, and time after extubation until rescue analgesia in groups TB (treatment: tramadol and bupivacaine), MB (positive control: morphine and bupivacaine), and B (negative control: bupivacaine)

Time	Group TB (mean±SE)	Group MB (mean±SE)	Group B (mean±SE)
Elapsed time between epidural administration and surgery (min)	35.00±1.50	35.41±1.99	34.58±4.78
Surgical time (min)	45.00±3.94	58.75±3.02	41.25±2.31
Elapsed time between epidural and extubation (min)	90.83±4.21	103.75±2.76	87.50±4.19
Anesthetic time (min)	104.16±3.83	115.41±2.25	102.50±3.76
Time after extubation until rescue analgesia (h)	14.00±0.42	21.75±0.84	6.30±0.47

Chapter V

Conclusion, Discussion, Comment

Conclusion

This study compared the epidural analgesic efficacy of bupivacaine, the combination of bupivacaine with either tramadol or morphine in 36 healthy dogs undergoing surgical correction of patellar luxation grades 2 and 3. All dogs were randomly allocated into 3 treatment groups (n=12 for each group) and received epidural drug administration as follow. Group B received 0.5% bupivacaine 0.16 ml/kg added with NSS to a total volume of 0.2 ml/kg; Group MB received 0.1 mg/kg morphine (morphine 2.5 mg/ml) added with 0.5% bupivacaine to a total volume of 0.2 ml/kg; and Group TB received 2mg/kg tramadol (tramadol 50 mg/ml) added with 0.5% bupivacaine to a total volume of 0.2 ml/kg. There were no significantly differences ($p>0.05$) of average heart rate, $ETCO_2$, ET_{iso}, systolic blood pressure, and SpO_2 during surgery. All measured parameters were also within the normal reference ranges throughout surgery. Average duration of postoperative analgesia was significantly longer in group MB (21.75±0.84 h) than in groups TB (14.00±0.42 h) and B (6.3±0.47 h). Average duration of postoperative motor deficit was also significantly longer in group MB (4.75±0.89 h) than groups TB (2.75±0.52 h) and B (2.25±0.03 h) with no difference between the latter 2 groups. The adverse effects observed in this study were hypersalivation and urine retention. Hypersalivation was observed in 1, 3 and 6 dogs in groups B, MB, and TB, respectively. One dog in MB group demonstrated urine retention. In conclusion, the duration of postoperative analgesia was longest in group MB followed by group TB and B, respectively. The addition of tramadol to bupivacaine could provide longer postoperative analgesia than bupivacaine alone. The combination of tramadol-bupivacaine provides adequate postoperative analgesia for up to 14 h with minimal side effects and can be safely used in substitution of morphine in the situation that controlled substance like morphine is not available.

Discussion

All treatment groups in this study demonstrated the ability in reducing isoflurane MAC (Minimum Alveolar Concentration) in dogs during surgical manipulations. The MAC of isoflurane in dogs (mean±SD) from various studies were 1.15±0.02% (Mattson et al., 2006), 1.19±0.15% (Credie et al., 2010), and 1.2±0.18% (Machado et al., 2006). In general, the amount of inhalation anesthetics required for achieving surgical plane of anesthesia is 1.2-1.4 MAC (Steffey and Mama, 2007). In the present study, the end-tidal isoflurane concentrations during surgery (mean±SE) were 0.74±0.05%, 0.86±0.05%, and 0.74±0.05% for groups TB, MB, and B, respectively. However, various factors including ambient pressure conditions (Steffey and Mama, 2007), opioids (Machado et al., 2006; Credie et al., 2010), and hypovolemic conditions (Mattson et al., 2006) may alter the MAC of isoflurane in dogs.

The reduction in amount of anesthetic requirement during surgery observed in all treatment groups in this study confirmed the results of previous study that epidural administration of bupivacaine (Hendrix et al., 1996; Almeida et al., 2007) and morphine-bupivacaine (Hendrix et al., 1996; Troncy et al., 2002; Kona-Boun et al., 2006) were capable of reducing the amount anesthetic used to achieve surgical plane of anesthesia. The reduction in amount of anesthetics consumed during surgery was beneficial to the animal, since the adverse effects associated with anesthetics occurred in a dose dependent manner (Steffey and Mama, 2007).

The measured parameters (heart rate, systolic blood pressure, oxygen saturation and end-tidal carbon dioxide) during surgery of all groups were within normal reference ranges, indicating that epidural administration of all drugs used in this study was safe and could be used in clinical setting.

Duration of adequate postoperative analgesia (mean±SE) was 14±0.42 h for group TB and was longer than group B. This finding was in consistency with those found in human pediatrics undergoing inguinal herniorrhaphy (Senel et al., 2001; Majid and

Mohammad, 2004; Prakash et al., 2006; Kartalov et al., 2008; Taheri et al., 2010) that the addition of tramadol to bupivacaine could provided longer postoperative analgesia than bupivacaine alone.

The duration of adequate postoperative analgesia (mean±SE) for group MB was 21.75±0.84 h. The duration of postoperative analgesia of epidural morphine-bupivacaine combination in the present study was consistent to those found in the previous study in dogs (Troncy et al., 2002). The duration of postoperative analgesia of the combination (mean±SD) in that study was 20.2±0.7 h.

The duration of sufficient postoperative analgesia (mean±SE) for group B was 6.3±0.47 h. The duration of postoperative analgesia in the present study was consistent to those reported in literature that epidural bupivacaine could provide analgesia for 4-6 h (Grimm and marks, 2005).

Duration of postoperative motor deficit was significant longer in group MB, but no statistical difference was detected between groups TB and B. This finding confirmed the result of the previous study (Troncy et al., 2002) that epidural morphine-bupivacaine produced longer postoperative motor deficit than bupivacaine. However, the duration of postoperative motor deficit resulted from the combination found in the previous study (9.1±0.3 h) was longer than that found in the present study (4.75±0.89 h). This may occur as a result of lower dose of bupivacaine (0.8 mg/kg) used in this study in comparison to that (1mg/kg) used in the previous study. Since, the duration of motor blockade of bupivacaine was dose dependent (Gomez de Segura et al., 2009).

Although average age in group TB was statistically significant younger than groups MB and B, it seemed to be clinically insignificant, since all dogs were not pediatrics (Hosgood, 2001; Mathews, 2005) and healthy according to physical examination, complete blood count, and blood chemistry profiles.

Surgical time, anesthetic time, and elapsed time between epidural administration and endotracheal extubation were significantly longer in group MB than in groups TB and B, due to the inability to control surgical time, since it depended on the degree of difficulty in correction of patellar luxation in clinical setting. However, this prolonged time seemed to be clinically insignificant, as dogs in group MB still demonstrated the longest elapsed time between endotracheal extubation and first postoperative tramadol administration. Thus, the MB group showed the best ability in controlling postoperative pain in this study.

No statistical difference of duration of postoperative sedation was observed among groups. This may occur as a result of the sedative effect induced by the premedicated drugs, namely acepromazine and tramadol. As this combination could provide sedation for at least 90 min with peak sedative effects occur within 30-45 min after administration (Monteiro et al., 2009).

The only adverse effect observed in the TB and B groups was hypersalivation, whereas in the MB group both hypersalivation and urinary retention were observed. However, the adverse effects associated with epidural morphine-bupivacaine found in the present study were less than those found in the previous study (Troncy et al., 2002). In that study, the adverse effects associated with epidural morphine-bupivacaine were mild cardiovascular and respiratory depression, vomiting, urinary retention, and pruritus. This may occur as a result of far less number of dogs (n=12) in the present study compared to those (n=196) in that study.

Comment

Epidural administration of morphine-bupivacaine provided longest postoperative analgesia (mean±SE) (20.2±0.7 h) followed by tramadol-bupivacaine (14±0.42 h), and bupivacaine (6.3±0.47 h). Thus, the combination of tramadol and bupivacaine should be used in substitution of morphine-bupivacaine in situation that controlled substance, as morphine, cannot be obtained. However, more studies needed to be done to verify the pharmacokinetics and pharmacodynamics of epidural tramadol-bupivacaine in dogs.

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Appendix

Table 12. Complete blood count and blood chemistry profiles of dogs in tramadol-bupivacaine group

Parameters	Iris	Sydney	Sydney	Yogi	Money	Sugus	Suchi	Pangpond	Tiger	Tongrioy	Sunny	Almond
R.B.C. (per µl)	6.5	8	7.3	5.3	6.5	6	5.5	6	7.9	7	7	6.7
Hemoglobin	14	17	18	14	115	16	15	16	16.3	16	18	12.7
Hematocrit	38	50	55	44	45	49	37	48	49	49	59	37
Plate count (per µl)	768	401	250	152	204	280	163	180	281	265	393	643
W.B.C. (per µl)	17,400	6,600	6,400	7,900	10,400	21,000	7,600	11,800	6,500	11,000	10,000	10,600
Neutrophils (%)	64	79	65	52		61	52	70	65		71	60
Bands (%)						3		1			2	
Eosinophils (%)	9		7	3		12	1	2	5		2	1
Basophils (%)												
Lymphocytes (%)	26	16	25	42		19	44	21	28		20	38
Monocytes (%)	1	5	3	3		5	3	6	2		5	1
SGPT (Units)	35	24	40	41	87	36	35	32	61	65	24	57
Alk.P/tase (IU/L)	52	47	100	160	40	42	87	103	84	196	30	90
BUN (mg%)	27	18	17	20	20	18	30	24	24	32	15	24
Creatinine (mg%)	0.9	0.6	0.8	0.9	0.8	0.7	1	0.6	0.6	0.8	0.5	1
Total protein (g%)	7	7.5	6.8	6.0	7.0	8.4	7.0	7.5	7.0	7.5	9.0	7.2

Table 13. Complete blood count and blood chemistry profiles of dogs in morphine-bupivacaine group

Parameters	Buffy	Money	Metung	Raene	Toalek	Lucky	Rangwal	Cherry	Money	Moohgling	Moohyong	Coca Cola
R.B.C. (per µl)	6	6.2	7	9	6.3	7	7.8	7.7	7	6	7	6.5
Hemoglobin	16	15.5	18	20	16	15	11	17	17	16	14	11
Hematocrit	48	47	54	53	43	45	47	48	52	48	45	40
Plate count (per µl)	327	398	270	114	447	130	226	261	204	288	160	445
W.B.C. (per µl)	14,600	9,000	14,500	9,300	12,400	11,600	11,600	10,900	10,400	10,700	9,500	13,300
Neutrophils (%)	80	70	60	60	67	80		73		66	75	64
Bands (%)								1		4	1	
Eosinophils (%)	2	4	8	10	4	2		2				2
Basophils (%)												1
Lymphocytes (%)	16	24	28	26	28	15		23		24	20	32
Monocytes (%)	2	2	4	4	1	3		1		6	4	1
SGPT (Units)	32	100	107	44	102	34	97	41	112	110	92	33
Alk.P/tase (IU/L)	74	133	30	84	100	40	71	98	40	210	17	108
BUN (mg%)	10	12	14	28	13	15	28	21	20	25	16	23
Creatinine (mg%)	0.9	0.7	0.6	0.5	1.0	0.6	0.7	0.7	1	0.4	0.5	0.6
Total protein (g%)	7.0	6.4	6.5	7.0	8.4	8.8	8.0	7.2	7.0	8.0	7.2	6.8

Table 14. Complete blood count and blood chemistry profiles of dogs in bupivacaine group

Parameters	Pepo	Pocky	MeMe	Tiger	Toalek	Pringgy	Chitrawee	Chivas	Bogchew	Baby	Toru	Somaoo
R.B.C. (per µl)	7.4	6.2	7.8	6.2	6.3	5.5	6.7	7.6	7	7.9	7	6.5
Hemoglobin	17	15	19	15	17	13	12.7	15.8	18	16	13	14
Hematocrit	51	45	47	47	48	44	45	49	58	51	41	45
Plate count (per µl)	189	227	413	305	365	232	643	308	321	282	370	142
W.B.C. (per µl)	11,000	9,300	9,800	8,300	12,000	9,300	10,100	8,800	8,000	4,700	8,700	9,100
Neutrophils (%)	79	71	54	59	64	76	60	55	80	54	60	
Bands (%)		3			4							
Eosinophils (%)	3	14	1	5	4	5	1	2		5		
Basophils (%)												
Lymphocytes (%)	12	10	42	33	22	10	38	42	15	36	21	
Monocytes (%)	6	2	3	3	6	9		1	5	5	3	
SGPT (Units)	53	50	110	80	70	100	57	50	34	53	40	19
Alk.P/tase (IU/L)	38	38	111	122	92	172	90	100	40	18	100	400
BUN (mg%)	17	10	13	37	8	32	20	24	22	18	24	21
Creatinine (mg%)	0.9	0.8	0.6	0.7	0.8	0.7	0.7	0.9	0.7	1	0.7	0.6
Total protein (g%)	8.0	7.0	6.5	8.0	7.4	7.0	6.4	7.1	6.4	7.0	7.0	7.0

Biography

Miss Nadhapat Bunnag was born on 14 September 1981 in Bangkok. She got her bachelor degree, Doctor of Veterinary Medicine (1st Class Honours), from Faculty of Veterinary Science, Chulalongkorn University in academic year 2004. One year after her graduation, she began her carrier as instructor at the Department of Surgery, Faculty of Veterinary Science, Chulalongkorn University. She has enrolled in the Degree of Master of Science Program in Veterinary Surgery since academic year 2008.