Evaluation of epidural morphine and incisional bupivacaine for analgesia following hemilaminectomy in the dog

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ABSTRACT

A blind, placebo – controlled clinical trial was performed to evaluate the postoperative analgesic effect of topically administered, intraoperative, epidural morphine (Duramorph™) and intramuscular infiltration of the incision site with bupivacaine prior to closure of the skin in dogs undergoing hemilaminectomy for Hansen type I Intervertebral Disk Disease (IVDD). Thirty-three dogs were randomly allocated into four treatment groups: epidural Duramorph™ with incisional bupivacaine (DUR/BUP), epidural saline with incisional bupivacaine (SAL/BUP), epidural Duramorph™ with incisional saline (DUR/SAL), and epidural saline with incisional saline (SAL/SAL). All dogs were premedicated with a standard protocol and were anesthetized with propofol and isoflurane. After surgery, scores were assigned using a visual analog scale (VAS) for both pain and sedation and a composite pain scale (CPS). In addition, a von Frey anesthesiometer was used to determine pain thresholds at 1 cm and 3 cm from the surgical incision line (primary hyperalgesia) as well as on the lateral aspect of the stifle (secondary hyperalgesia). Assessments were carried out at fixed intervals over the 48 hour postoperative period. Significant differences were found between those groups treated with the epidural Duramorph™ and those that received epidural saline. Those dogs in the DUR/BUP and DUR/SAL groups exhibited lower von Frey pain thresholds and higher VAS and CPS scores

than the SAL/BUP and SAL/SAL groups. The administration of bupivacaine had no significant effect on any measured outcome. The authors conclude that topically administered epidural Duramorph™ and intramuscular incisional bupivacaine do not enhance analgesia following hemilaminectomy in the dog.

DEDICATION

This manuscript is dedicated to the loves of my life, my best friends, my babies, Murray and Harrison. Without their unconditional love and continued sacrifice, I would not have been able to accomplish the goals that I had set out to achieve. I only hope I have made them proud and that one day I feel worthy.

'He is your friend, your partner, your defender, your dog. You are his life, his love, his leader. He will be yours, faithful and true, to the last beat of his heart. You owe it to him to be worthy of such devotion'.

---Anonymous

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INTRODUCTION

Intervertebral disk disease (IVDD) is one of the most common causes for canine emergency presentation to veterinarians. This disease process causes debilitating pain and neurologic dysfunction and is the most common cause for thoracolumbar myelopathy with paraspinal hyperesthesia in dogs[1,2]. IVDD is a manifestation of the degenerative changes present within the intervertebral disk and is typically a disease of chondrodystrophic breeds, with a reported incidence of 73% between three and six years of age[3].

Intervertebral disk disease is categorized by Hansen[4,5] in two ways: Hansen type I disease is distinguished by herniation of the nucleus material into the spinal canal as it extrudes through the dorsal annulus, and Hansen type II is characterized by annular protrusion causing shifting of the central nuclear material and fibrous disk degeneration [Figure 1][4,5]. Funkquist originally described a third type of disk extrusion (type III) which consists of nucleus extrusion through the dura into the spinal cord[6]. Dogs affected with Hansen type I disk disease typically present with an acute onset of pain and associated neurologic dysfunction. The incidence of Hansen type I IVDD in the thoracolumbar region is about 80%[5,7] with the thoracolumbar junction (T12-T13, T13-L1, L1-L2) accounting for 65% of all thoracolumbar lesions[5,7].

Surgical management is recommended in dogs with thoracolumbar IVDD presenting with spinal pain or paraparesis that is unresponsive to conservative management, those with recurrence or progression of clinical signs, and those with paraplegia with intact deep pain perception or paraplegia without deep pain perception for less than 48 hours duration[2,8]. The aims of surgery

are spinal cord decompression (dorsal laminectomy or hemilaminectomy) and removal of extruded disk material from the extradural space with or without fenestration. The overall success rate (defined as return to function) after decompressive surgery ranges from approximately 60% to 95% depending on the duration of clinical signs prior to treatment and the severity of neurologic dysfunction at the time of presentation[9-14].

Post operative pain management of these patients is an integral component of their care. Though protocols vary depending on surgeon and clinic, parenteral opioid administration is widely used for postoperative analgesia in hemilaminectomy patients. This method of pain control may be inadequate for some patients and produce undesirable[15] side effects such as respiratory depression, emesis, ileus and dysphoria[16]. Alternative modalities for treating pain associated with IVDD and surgery have been investigated in humans and include the topical epidural administration of opioids as well as the administration of local anesthetics[17-36]. Topically administered epidural opioids reportedly provide excellent analgesia while reducing the incidence of side effects[18,34-37]. Epidural infusions of fentanyl also reduced pain scores and total consumption of morphine in humans undergoing lumbar laminectomy.[24,38,39] Lidocaine, injected intramuscularly to the incisional area in dogs undergoing routine ovariohysterectomy reduced post operative pain scores.[40] Additionally, the injection of bupivacaine into the incisions of humans following lumbar spinal surgery reduced pain scores and post operative morphine consumption[20,23,29,41-44]. The combination of both epidural morphine and incisional bupivacaine infiltration has been effective in reducing post operative pain in humans undergoing

surgery for lumbar disk disease[29,34]. However, the combination of techniques has not been evaluated in dogs with IVDD.

The objective of the current study was to determine if the topical application of epidural morphine in combination with local incisional injection of bupivacaine would provide enhanced analgesia following thoracolumbar hemilaminectomy for type I IVDD in dogs.

CHAPTER 1: Literature Review

A: *Intervertebral Disk Disease (IVDD)*

A1a. *Anatomy* – Intervertebral Disk

The intervertebral disk is composed of three regions: the outer annulus fibrosus, the inner nucleus pulposus, and the cartilagenous end plate[4] [Figure 2]. The annulus is made up of collagen (type I predominantly)[45] fibers arranged in layers or lamellae, which are thicker and more numerous ventrally. The inner lamellae of the annulus blend with the nucleus pulposus with a thin transition zone between the two[4]. The annulus is supplied with pain fibers mainly in the outer laminae[46]. The nucleus is highly hydrated and is unorganized in its fibrillar network[4]. Water is the principle component of the nucleus pulposus, making up 80-85% of its content[47]. This water is bound to the proteoglycan constituents (keratin sulfate, chondroitin sulfate, and hyaluronic acid) that make up the ground substance within the disk[45,48-50]. In normal dogs, this gelatinous nucleus persists in about 75% of disks at four years of age and less than 19% in those patients over 7 years of age, with keratin sulfate increasing relative to chondroitin sulfate.

Chondrodystrophic breeds can lose this gelatinous nucleus within the first year[4]. In these breeds degeneration is accelerated with disks undergoing chondroid metaplasia as early as 2 months after birth. This chondrification includes a decrease in glycosaminoglycans (component of the proteoglycan) and an increase in the collagen content[4,5,50-54]. Mineralization of disks has been observed in chondrodystrophic puppies as young as five months of age[47] and the incidence increases with age[54].

A1b. *Anatomy - Supporting Structures*

Supporting structures associated with influencing intervertebral disk extrusion include the longitudinal and intercapital ligaments and the cartilagenous end plates. The dorsal longitudinal ligament is attached to the vertebral bodies throughout the spine and widens dorsal to each disk. The ventral longitudinal ligament is attached to the vertebrae and disks and is more developed from the mid thoracic region caudally. The intercapital ligament extends from the head of one rib over the dorsal annulus, but under the dorsal longitudinal ligament, to the head of the opposite rib [Figure 3] [55]. This structure is regularly absent from the first, eleventh, twelfth and thirteenth ribs and is sometimes absent from the tenth as well. Free nerve endings have been found in spinal ligaments of many species including humans and dogs[46]. In humans and dogs the sinuvertebral nerve is responsible for innervation of the outer third of the annulus fibrosus[56]. Thin layers of hyaline cartilage that cover the vertebral body epiphyses form the cranial and caudal boundaries of each disk, the end plate[55]. Diffusion across the cartilagenous end plate supplies the disk with nutrients and it is thought that occlusion of the end plate may lead to disk degeneration[57-59].

A1c. *Anatomy - Meninges and Sinuses*

There are three membranous layers that serve to protect the spinal cord as well. The arachnoid membrane and the pia mater, collectively known as the leptomeninges, and the dura mater make up these layers. There are thickenings of the pia mater on each side of the spinal cord, which are called the denticulate ligaments; these ligaments traverse the subarachnoid space and attach to

the dura mater thereby suspending the spinal cord within the surrounding cerebrospinal fluid[55]. The meninges along with the epidural fat within the spinal canal facilitate the protection of the spinal cord during normal movement. The internal vertebral venous plexus, or vertebral sinuses, extend bilaterally along the floor of the vertebral canal from the skull to the caudal vertebrae. They are largest in the cervical region and lie against the pedicles of the vertebral arches. In the thoracolumbar region, they course more medially, diverging at the disk spaces and converging over the vertebral body[55,60].

The intervertebral disks are meant to provide flexibility to the vertebral column and act as shock absorbers for the spine. Collectively, the three components of the disk (annulus, nucleus, and end plate) work in concert to permit flexibility of the spine while under physiologic loads and impart stability when subject to deforming loads[61,62]. The capacity to absorb shock is diminished by age and degenerative changes.

A1d. *Anatomy - Spinal Cord*

Sensory information is collected from the peripheral nervous system and transmitted to the brain via sensory axons, the cell bodies of which lie in the dorsal root ganglia. Central projections of these axons ascend the spinal cord to the brain and are therefore called ascending sensory tracts[63]. Proprioception is transmitted in the tracts of the dorsal and lateral funiculi to the somesthetic cerebral cortex or cerebellum. Temperature and superficial pain sensation are transmitted by myelinated fibers of several tracts including the lateral spinothalamic in the lateral funiculus. Deep pain sensation, or nociception, is carried by smaller, nonmyelinated fibers,

particularly in the propriospinal and spinoreticular tracts. These fibers lie more centrally within the spinal cord and are therefore less prone to injury, except in the case of severe, extensive cord damage[63].

The upper motor neuron (UMN) and lower motor neuron (LMN) systems are responsible for transmission of motor function[63]. The cell bodies of the LMN lie in the ventral gray matter of the spinal cord. The axons leave the spinal cord in ventral nerve roots and pass through the brachial and lumbosacral plexuses to form the peripheral nerve trunks of the limbs[63]. These neurons are the effector portion of the reflex arc. The sensory arm of the reflex arc is a sensory neuron which arises in the periphery, enters the dorsal root and projects to the LMN[63]. Function of flexor muscles is facilitated by the corticospinal and rubrospinal tracts. The corticospinal tracts arise in the cerebral cortex, and most decussate at the spinomedullary junction and descend in the lateral corticospinal tracts of the lateral funiculi. Fibers that do not decussate descend in the ventral funiculi. The rubrospinal fibers originate in the red nucleus of the brainstem, cross midline and descend in the rubrospinal tract of the lateral funiculus[63]. The vestibulospinal tracts and the reticulospinal tracts also influence motor function. The function of extensor muscles is facilitated by these tracts, which lie in the ventral funiculi. The vestibulospinal fibers arise in the ipsilateral vestibular nuclei. They facilitate extensors and inhibit flexors on the ipsilateral side, and have the opposite effects on muscles of the contralateral limb[63].

The white matter tracts of the spinal cord are composed of nerve fibers of varying size. Most of these fibers are myelinated. The largest myelinated fibers are the most rapidly conducting and

transmit proprioception. Motor fibers are intermediate-sized myelinated fibers and pain fibers are the smallest with varying myelination. Ascending proprioceptive tracts are located more superficially within the cord while those carrying pain perception are located more deeply. The larger and more peripheral fibers are more susceptible to injury, which correlates with the progression of clinical signs associated with spinal cord compression and IVDD. Mildly compressive lesions will cause loss of proprioception, while more severe lesions can cause loss of voluntary motor and nociception[63].

A2a. *Background - Diagnosis*

Based upon signalment and clinical presentation a presumptive diagnosis of IVDD can be made. However, other disease processes that may present in a similar manner include: diskospondylitis, inflammatory disease (GME), spinal trauma, and spinal neoplasia. Spinal radiographs should be performed in all dogs suspected of having IVDD. This imaging modality can help to rule out diskospondylitis, spinal fractures, and vertebral neoplasia. Radiographs of the spine may require general anesthesia for appropriate positioning, which can be done prior to myelography. The radiographic signs associated with IVDD include narrowing or wedging of the intervertebral space, narrowed articular process joint space, small intervertebral foramen, increased opacity of the intervertebral foramen, and calcified material within the vertebral canal[64,65]. However, the accuracy of determining the primary sites of disk protrusion using survey radiographs is reportedly 51-61%[64,66]; secondary sites have an even lower accuracy[64]. This modality is not considered adequate to target a specific intervertrebral disk space for surgical approach to the affected region.

Myelography or advanced imaging (CT/MRI) must be performed in order to make a definitive diagnosis of extradural compression of the spinal cord. These imaging techniques are typically reserved for those patients that would be candidates for surgery. Myelographic findings correlate with surgical findings in 87-98% of cases[65,67]. Myelography is performed by intrathecal injection of radiographic contrast medium to allow a view of the spinal subarachnoid space and the outer margins of the spinal cord[68]. Percutaneous injection of non-ionic iodinated contrast media[68-70] (i.e. Iohexol) is typically performed at the L4-L6 disk spaces. It is recommended that cerebrospinal fluid be collected prior to injection of contrast to allow for analysis if no lesion is detected with myelography. During and immediately following injection of the contrast medium, flow of contrast can be assessed by fluoroscopy or sequential radiographs may also be taken[68]. Lateral, dorsoventral, and oblique radiographic views should be evaluated if fluoroscopy is not available in order to aid in determining the side of extrusion[68,71]. Complications associated with myelography include post-contrast asystole, post-contrast seizures, meningitis, deterioration of premyelographic neurologic status, and iatrogenic trauma to the cord during placement of the spinal needle for injection[72-75]. Though myelography can distinguish between extradural and intradural lesions, the exact nature of the mass (whether it is mineralized disk material or neoplasia) cannot be determined with myelogrpahy alone. Myelographic findings suggestive of extradural spinal cord compression secondary to disk herniation include dorsal deviation of the ventral subarachnoid contrast column and thinning of the dorsal contrast column dorsal to a disk space on the lateral view [Figure 4] [60,65,67,68]. On the ventrodorsal view this appears as attenuation of one or both of the lateral

subarachnoid contrast columns [Figure 5] [60,65,67,68]. Findings on myelography associated with spinal cord swelling may also aid in establishing prognosis[76].

Computed tomography (CT) and magnetic resonance imagine (MRI) are more accurate than myelography for diagnosis of IVDD. These modalities are also less invasive as mineralized disk material shows clearly without the need for contrast. CT and MRI also allow easier determination of the side of the disk extrusion as compared to myelography and therefore facilitate better surgical planning. Both require general anesthesia and are more expensive than myelography. CT has the additional advantage of being faster than most MRI units. A heterogenous, hyperattenuating, extradural mass with loss of epidural fat are characteristic features of mineralized disk extrusions on CT images [Figure 6] [77]. Epidural hemorrhage appears as slightly more attenuating than spinal cord[77]. CT may be combined with myelography to allow visualization of the subarachnoid space, improve accuracy in differentiating intramedullary from extradural causes of spinal cord swelling, and definitively determine the location of herniated disk material[8]. In a recent retrospective study, CT had an 81.8% sensitivity for detection of the site of intervertebral disk herniation as compared to surgical findings[78].

MRI allows early recognition and classification of disk degeneration[79]. MRI findings consistent with disk degeneration include decreased signal intensity on T2-weighted images[79,80], as the intensity correlates directly with proteoglycan content[80]. In addition, the loss of the normal demarcation between the annulus fibrosus and the nucleus pulposus, in which the nucleus

appears as an ovoid area of high signal intensity compared to the relatively hypointense annulus, also indicates disk degeneration [Figure 7] [79]. Like CT, other findings on MRI suggestive of disk extrusion include disk fragmentation and displacement of epidural fat[79]. However, mineralization of disk cannot be diagnosed definitively by means of MRI. Changes associated with mineralization could be mistaken for other lesions[79]. MRI can also establish the presence of extradural hematoma with acute hemorrhage appearing as a region of low signal intensity on T2-weighted images[81]. However, the appearance of hemorrhage does change over time. If necessary, intravenous contrast can be given to establish whether a compressive lesion is scar tissue, neoplasia, or disk material. Findings on MRI may also be used to determine prognosis in dogs with thoracolumbar IVDD[82] by allowing assessment of soft tissue structures including spinal cord parenchyma and ligaments.

A2b. *Background - Management*

Spinal hyperpathia and neurological deficits of the pelvic limbs are features of thoracolumbar disk disease. In severe cases, urinary bladder dysfunction may also occur. Deficits range from back pain alone, to mild ataxia, or paraparesis to paraplegia, which may be accompanied by depressed or absent nociception caudal to the lesion[8].

Several classification schemes have been developed describing hyperesthesia and motor and sensory dysfunction in order to determine appropriate treatment options for dogs with acute spinal cord injury. Most of these systems are modifications of the Frankel scale, which was developed for humans with traumatic myelopathy[83]. This scale classified myelopathy based

upon the ability to move and feel the limbs. Veterinary modifications typically incorporate assessment of pelvic limb motor function and nociception with between 3 and 6 grades of injury[3,84-87]. Most recently, the Texas Spinal Cord Injury Scale (TSCIS) was described and evaluated for repeatability as a prognostic indicator for dogs with spinal cord injury[88]. The TSCIS included weighted scales for gait, proprioceptive positioning and nociception. However, this newly developed system has yet to gain wide acceptance.

Regardless of the scaling method used, indications for conservative or nonsurgical management of thoracolumbar IVDD include a first-time episode of spinal pain only or mild to moderate paraparesis and financial constraints[2,8]. Conservative management consists of strict cage rest, physical rehabilitation, and administration of analgesics, muscle relaxants, or anti-inflammatories[2,8]. The success of this type of management in ambulatory dogs with presumed thoracolumbar Hansen type I IVDD is reported to be between 82-88% and is about half of that (43-51%) for those dogs that are non-ambulatory[6,87,89-91]. Clinical recurrence rates in dogs that are conservatively managed range between 30 and 40%[90-93]. In addition, for 80% of those that exhibit recurrent clinical signs, this recurrence will occur within 2 years[3,6].

Surgical management is recommended in thoracolumbar IVDD cases with spinal pain or paresis that is unresponsive to conservative management, those with recurrence or progression of clinical signs, and those with paraplegia with intact deep pain perception or paraplegia without deep pain perception for less than 48 hours[2,8]. The aims of surgery are spinal cord

decompression and removal of extruded disk material from the extradural space with or without disk fenestration. This can be accomplished thorough hemilaminectomy, pediculectomy, or dorsal laminectomy[8]. All of these decompressive procedures are performed by a dorsal approach to the vertebral column. With the animal in sternal recumbency an incision is made on dorsal midline or slightly paramedian on the side of the lesion usually starting and ending three vertebral sites cranial and caudal to the site of the lesion. Subcutaneous fat and fascia are incised to the thoracolumbar fascia. The fascia and supraspinous ligament are incised to expose the multifidus musculature. Subperiosteal elevation and sharp dissection release the tendinous insertions on the spinous process and are continued laterally over the laminae to the articular processes. The origin of the multifidus musculature is removed from the articular process in a caudal to cranial direction. The muscle is elevated to the mammilary process and the tendon is incised from that point [Figure 8]. Self retaining retractors are placed to facilitate exposure. For additional exposure, the tendon of the longissimus musculature that inserts on the accessory process is transected [Figure 9] [94]. Hemilaminectomy is purported to allow better access to the ventral and lateral spinal canal than dorsal laminectomy, thereby improving the ability to remove disk material from this space while avoiding undue trauma to the spinal cord[95,96], however, no studies document the amount of disk material that remains in the canal following either procedure. It is further reported that while disk material is removed in 90% of dogs using either a dorsal approach or hemilaminectomy, those dogs undergoing hemilaminectomy have a better outcome[97]. Dorsal laminectomy has also been associated with the development of a constrictive laminectomy membrane, dense fibrous tissue that replaces the bone removed and binds to the dura and overlying muscles[96].

Hemilaminectomy requires the removal of one or more ipsilateral articular facets, lamina and pedicle [Figure 10][8,98] while dorsal laminectomy typically involves partial facetectomy in addition to removal of the spinal processes[8,98]. Pediculectomy, also described as minihemilaminectomy, spares the articular facets and the lamina[8]. The overall success rate (defined as return to function) after decompressive surgery ranges from approximately 60% to 95% depending on the duration of clinical signs prior to treatment and the severity of neurologic dysfunction at the time of presentation[9-14]. In dogs that have deep nociception present the prognosis for return to function ranges from 72-100%[9,11,13,97,99-103]. The mean time for nonambulatory dogs with intact deep pain sensation to become ambulatory following surgical decompression is reported to be between 10 and 13 days[9,11] with time to ambulation increasing with patient size[99]. Patients without deep pain sensation at time of presentation have a poorer prognosis for return to function, with an overall chance of recovery between 28 and 78%[12,14,104,105]. The variation in findings may be a result of the subjective nature of the assessment of deep nociception in these patients and the differences in categorization of a successful outcome in the literature. Further, 88% of dogs that initially present with absent nociception that return to ambulation have intermittent fecal or urinary incontinence[105].

Fenestration is the excision of the nucleus pulposus through a surgically created window in the annulus[3,8,106]. It has been suggested that disk fenestration at the site of extrusion and at distant sites may contribute to a lower recurrence rate following surgery. In 88% of cases that require

reoperation more than one month following initial surgery it is due to disk herniation at a distant site[107,108]. Further, the number of calcified disks at time of initial surgery has been found to be a risk factor for this recurrence[109]. Some surgeons and neurologists would argue that these reports support the merits of fenestration as a preventative measure. Others contend that the benefits are not outweighed by the risks of destabilization secondary to fenestration, subsequent herniation of disks at sites adjacent to fenestration, and the added dissection and therefore surgical time necessary to perform the procedure[110-113]. The overall recurrence rate for dogs undergoing hemilaminectomy with or without fenestration for IVDD is between 3 and 42%[12,86,96,108].

B: *Pain*

B1. *Physiology*

In particular, IVDD and the surgery to decompress the spinal cord are associated with moderate pain levels that, if untreated, can delay ambulation and physical therapy, prolong hospitalization and decrease quality of life. In order to develop a rational and effective pain management strategy a basic understanding of pain physiology is necessary. This includes the inciting stimuli, neural pathways, response to repeated or prolonged stimuli and the resultant systemic consequences of pain. Equally important is the ability to assess the degree of pain a patient is experiencing in order to determine if treatment is necessary and whether or not the chosen protocol is effective.

Nociception consists of the process of transduction, transmission and modulation of neural signals generated in response to noxious stimuli. It is a physiologic process that results in the conscious perception of pain[114].

In its simplest form, nociception can be considered as a three neuron chain with the first order neuron originating in the periphery and projecting to the spinal cord, the second order neuron ascending the spinal cord, and the third order neuron projecting to the cerebral cortex[114]. The first process of nociception involves the encoding of mechanical, chemical or thermal energy into electric impulses by nociceptors or primary afferent neurons. These are free nerve endings that function to preserve tissue homeostasis by signaling actual or potential tissue injury. These fibers are further classified as Aδ or C according to their stimulus sensitivities. Aδ fibers typically signal first pain which is characterized by a sharp, stinging, pricking sensation. This is typically well localized and transient. Whereas C fibers signal second pain or slow pain and are recruited when the stimulus is of sufficient magnitude. This is described as a more diffuse and persistent burning sensation extending beyond the termination of the acute painful stimulus[114]. These pain fibers are located throughout the skin, peritoneum, periosteum, subchondral bone, joint capsules, muscles, tendon, fascia and viscera[114]. The cell bodies of these nerve fibers are contained within the dorsal root ganglia where they extend to synapse with the dorsal horn neurons within the spinal cord[114]. It is within the spinal cord that the integration and modulation of this input initially occurs. Within the dorsal horn the communication of nociceptive input between various neurons is carried out with chemical signaling. This signaling is mediated by excitatory and inhibitory amino acids (glutamate, aspartate) and neuropeptides (substance p,

neurotensin, cholecystokinin)[114]. The nociceptive input is further transmitted to supraspinal centers by projection neurons extending through several ascending tracts, primarily the spinothalamic tract. Nociceptive neurons have been identified in portions of the medulla, pons, mesencephalon (midbrain), diencephalon (thalamus, hypothalamus), and cerebral cortex[114]. It is here that the conscious perception of pain occurs.

In addition to ascending nociceptive pathways, there are powerful descending pathways that are able to modulate the pain response, up regulating or down regulating it. The regions responsible for this modulation include the dorsal horn, the periagueductal gray matter (PAG) of the midbrain, the rostroventral medulla and pons of the brainstem, and the thalamocortical structures[114,115]. It is thought that the PAG also plays a role in the endogenous analgesia system[114].

B2. *Implications*

Pain has multisystemic implications with effects on the cardiovascular, digestive and neuroendocrine systems. It induces segmental and suprasegmental reflex responses that result in increased sympathetic tone, vasoconstriction, increased systemic vascular resistance, increased cardiac output as a result of increased stroke volume and heart rate, increased myocardial work with resultant increased oxygen consumption and metabolic rate, decreased gastrointestinal and urinary tone and increased skeletal muscle tone[114]. The endocrine response includes increased secretion of cortisol, antidiuretic hormone, cyclic AMP, catecholamines, rennin, angiotensin II, aldosterone, and glucagon with decreased secretion of insulin and testosterone. The result is a

catabolic state characterized by hyperglycemia, protein catabolism and lipolysis, renal retention of water and sodium with potassium excretion, and decreased glomerular filtration rate[114].

Finally at the cortical level, the anxiety caused by the painful state may contribute to increased blood viscosity, prolongation of clotting times, fibrinolysis, and platelet aggregation[114]. These effects constitute the typical stress response and in a clinical setting this has an impact on patient morbidity and may prolong healing. In some cases, pain can be severe enough to cause physiologic states consistent with shock. Pain can also cause psychological manifestations including depression, anorexia, and hiding or avoidance behavior or aggression.

The presence or absence of these stress related changes forms the basis for most pain assessment systems.

B3. *Sources*

The management of pain following laminectomy can be challenging. There are several factors that contribute to this difficulty including the potential for pain of several days duration prior to surgery, and the varied sources of pain i.e. neuropathic (radicular, diskogenic), periosteal, and soft tissue. In addition, the inability to decipher painful responses in veterinary patients, especially those that may be considered hyperalgesic, makes it more difficult for the examiner to interpret their behavior or responses and to treat them appropriately. In surgical patients the painful stimulus is not transient and may be associated with significant tissue inflammation or nerve injury. This is considered pathologic pain or clinical pain and is characterized by ongoing discomfort and abnormal sensitivity[116]. Neuropathic pain results from direct damage to the nervous system and is characterized by altered sensory processing of stimuli and its associated

hypersensitivity, termed, hyperpathia[117-119]. It is common for dogs with intervertebral disk disease to exhibit signs of hyperpathia, including generalized pain and an exaggerated pain response. Sources of pain in dogs with IVDD include direct mechanical stimulation or chemically mediated sensitization of nociceptors. Direct compression of dorsal root ganglion, from dorsolateral disk protrusion may lead to intraneural edema and altered blood supply to the dorsal root ganglion resulting in abnormal neuronal activity and pain[56]. Other sources of pain include dorsal or ventral longitudinal ligament, peripheral annulus (diskogenic), meninges, and periosteum[56]. Additionally, a variety of substances are released from degenerated disks. These include glycosaminoglycans and lactic acid. This leakage can cause an inflammatory response in the arachnoid and epidural spaces resulting in the production of inflammatory chemical mediators. This can further lead to hyperalgesia through peripheral sensitization[56]. Several inflammatory mediators, including phospholipase A_2, interleukin-1α and β, interleukin-6, and tumor necrosis factor α are elevated in prolapsed human disks or have been documented in the region of disk prolapse in elevated concentrations[56,120]. The duration of pain experienced by these patients prior to surgery makes it more of a challenge to provide adequate analgesia in the post-operative period. Of particular importance in the management of pain is the fact that nociceptors have the unique ability to adapt to repeated suprathreshold noxious stimuli by lowering their threshold, resulting in enhanced response to subsequent stimuli. This adaptation is termed sensitization[114,115]. As in peripheral nociceptors, these sustained afferent impulses produce an altered response centrally, in spinal cord dorsal horn neurons, as well[116-118,121-127]. This central sensitization or wind up has had a major impact on pain management strategies,

particularly in surgical patients, and the advent of pre-emptive analgesia. A key receptor thought to be involved in this process is the glutamate-activated N-methyl-D-aspartate (NMDA) receptor. Phosphorylation of this receptor increases its responsiveness to glutamate, one of the principal excitatory mediators involved in signal transduction and processing in thalamocortical systems[114]. Surgical pain from tissue inflammation or trauma is considered acute pain. Acute pain plays a biologically adaptive role by facilitating tissue repair and healing. This is achieved by hypersensitivity of the injured area (primary hyperalgesia) as well as the surrounding tissues (secondary hyperalgesia) so that contact with external stimuli are avoided and the repair process can proceed[116]. Most clinical pain syndromes are complex and involve more than one type of pain so it can be difficult to predict the mechanisms mediating pain in any given case. In order to minimize the debilitating pathologic pain experienced by clinical patients various strategies may be required.

C: *Analgesia*

C1. *Multi-modal analgesia*

Multi-modal or balanced analgesia is an approach that attempts to alleviate pain by combining treatment strategies and classes of analgesics. The goal is to enhance the effect that each treatment modality would provide alone through synergistic and additive effects of the combination, while decreasing the necessary dose and associated side effects of each analgesic used alone[115].

Nociceptors transduce noxious stimuli through the influx of Na^+ and K^+ ions with initiates depolarization. If depolarization is sufficient in magnitude, voltage gated Na^+ channels are activated, further depolarizing and causing action potentials. The resultant action potentials are conducted from the periphery to the central nervous system along axons of primary afferent nociceptive fibers[114]. Local anesthetics, such as lidocaine and bupivacaine, are classic Na^+ channel blockers and are considered to be primary analgesic agents[114,115]. The major mechanism of action of local anesthetics is the stabilization of peripheral nerve membranes. Additionally, local anesthetics affect many membrane-associated proteins in tissue and can inhibit the release and action of prostaglandins and lysosomal enzymes, which sensitize or stimulate nociceptors and promote inflammation[128]. Serving as the first relay point for somatic sensory information going to the brain, the dorsal horn neurons can also be targeted by analgesics. The principle analgesics that act in the dorsal horn are the opioids, the α-2 agonists, and the non-steroidal anti-inflammatory drugs (NSAIDS). A dense concentration of opioid receptors exists in the dorsal horn and the activation of these receptors can have both pre- and post- synaptic effects. Presynaptically, decreased Ca^{2+} influx reduces the release of excitatory transmitter substances, such as substance P, from primary afferents. This inhibits nociceptive transmission[115]. At the post synaptic level, enhanced K^+ efflux causes hyperpolarization of projection neurons, inhibiting ascending nociceptive pathways. Belonging to the same family as opioid receptors, α-2 receptors in the dorsal horn have a similar mechanism of action as for opioids. NSAIDS have both central and peripheral effects. Their antiprostaglandin characteristics make them appropriate for minimizing the peripheral sensitization of nociceptors and their inhibition of cyclooxygenase (COX) within the spinal cord give them centrally acting

analgesic attributes as well. Opioids play the most significant role in action on descending nociceptive modulatory pathways. This is accomplished through their actions at multiple levels including the PAG and the dorsal horn[115]. It has been suggested that there is a decreased efficacy of the descending inhibitory pathways in animals with neuropathic lesions[129,130]. Previous studies have demonstrated a reduced sensitivity to intrathecal or intravenous morphine consistent with decreased opioid receptor function[129,130]. In one study, descending inhibition was 50% lower in neuropathic animals as compared to normal controls[131]. Ketamine and other NMDA receptor antagonists (i.e. Amantadine) also play a role in analgesic therapy, as their effect reduces central sensitization and hypersensitivity[115].

Post operative pain management of surgical patients is an integral component of their care. Though protocols vary depending on surgeon and clinic, parenteral opioid administration is widely used for postoperative analgesia in hemilaminectomy patients. This method of pain control though, may be inadequate for some patients and produce undesirable[15] side effects such as respiratory depression, emesis, ileus and dysphoria[16]. Alternative modalities for treating pain associated with IVDD and surgery have been investigated in humans and include the topical epidural administration of opioids as well as the administration of local anesthetics[17-36,132-143]. Topically administered epidural opioids provide excellent analgesia while reducing the incidence of side effects[18,34-37,144]. Epidural infusions of fentanyl reduced pain scores and total consumption of morphine in humans undergoing lumbar laminectomy.[24,38,39] Lidocaine, injected intramuscularly to the incisional area in dogs undergoing routine ovariohysterectomy

also reduced post operative pain scores.[40] Additionally, the injection of bupivacaine into the incisions of humans following lumbar spinal surgery reduced pain scores and post operative morphine consumption[20,23,29,41-44,145]. The combination of both epidural morphine and incisional bupivacaine infiltration was effective in reducing post operative pain in humans undergoing surgery for lumbar disk disease[29,34]. However, epidural morphine and incisional intramuscular injection of bupivacaine has not been evaluated for postoperative analgesia in dogs with IVDD undergoing hemilaminectomy.

As a hydrophilic opioid, morphine administered epidurally has a slow onset (30-60 minutes) and prolonged duration (6-24 hours) of action at below systemic doses. It provides analgesia without sensory, sympathetic or motor impairment. Though systemic absorption still occurs, the lower dosage does not typically result in systemic effects. In addition, its cranial spread in the epidural space is extensive due to its prolonged presence in cerebrospinal fluid which facilitates its actions on dermatomes distant to the site of injection. The injection of epidural morphine can be associated with complications including urine retention, intense pruritis, and iatrogenic spinal cord trauma or infection[146]. Bupivacaine, a local anesthetic, blocks the generation and conduction of nerve impulses by inhibiting voltage gated sodium channels thereby preventing cell membrane depolarization. As an aminoamide bupivacaine is lipophilic, highly protein bound, has a slow onset of action (20-30 minutes) and has a long duration of action (4-6 hours). Even distribution of local anesthetic into the tissues of a surgical site can sometimes be technically difficult and often results in uneven, or variable analgesia;[147,148] therefore, care should be taken to infiltrate each tissue plane within a surgical site so as to provide effective

analgesia. Infiltration of large volumes of local anesthetic agents may increase the risk of systemic absorption and side effects in people[149] but a 2 mg/kg dosage is less than the maximal safe dosage for most species (i.e., 2.2 mg/kg in small animals)[150] and only half the toxic dosage (4 mg/kg)[147] in dogs, and therefore is less of a concern. The side effects associated with intravascular injection of bupivacaine are primarily cardiovascular and central nervous system related including cardiac arrhythmias and seizures. However these side effects are uncommon with local intramuscular injection occurring only if inadvertent intravascular injection occurs[151].

C2. *Human Spinal Surgery Analgesia*

The injection of bupivacaine in peri-incisional tissues used alone or in conjunction with spinal or epidural analgesia in human patients undergoing spinal surgery has been investigated with varying results[21]. Inconsistent results may be related to poor clarification of the term wound infiltration, which may be used to describe both subcutaneous (only) and full-thickness intramuscular infiltration of the surgical incision[152]. A study of 60 patients undergoing lumbar diskectomy determined that local muscular injection of bupivacaine at the wound prior to closure significantly lowered pain scores and postoperative opioid consumption[29]. This beneficial effect was also found to be the case in a subsequent study of patients undergoing lumbar laminectomy[20]. A 2003 study evaluated the effect of spinal bupivacaine and epidural clonidine with or without incisional subcutaneous bupivacaine in patients undergoing lumbar laminectomy. Patients receiving the subcutaneous bupivacaine had lower pain scores and less need for rescue opioids. Interestingly, there was a synergistic effect between the epidural

clonidine and the subcutaneous bupivacaine, with lower scores in the group receiving the combination, than in the groups that received each treatment alone[43]. Another clinical trial evaluated postoperative lumbar laminectomy patients to establish whether there was a difference between the route of morphine administration (epidural vs. intrathecal) and whether administration of intramuscular bupivacaine alone was sufficient. There was no difference between groups receiving intramuscular bupivacaine and the groups that received saline. However, patients that received either intrathecal or epidural morphine had significantly better pain scores and less need for postoperative analgesics[34]. When peridural methylprednisolone (applied to spinal nerve roots during surgery) and intramuscular bupivacaine were compared to a placebo group undergoing lumbar spinal surgery, patients in the treatment group required less opioid analgesia post-operatively, had lower pain scores, and exhibited less nausea when compared to the placebo group[23].

Epidural and local analgesia have been investigated in veterinary patients undergoing various surgical procedures including fracture repair, tibial plateau leveling osteotomy (TPLO), ovariohysterectomy (OHE), celiotomy for procedures other than OHE, and total ear canal ablation[40,153-158]. In the largest case series which included 265 patients, the effect of pre-emptive, epidural morphine with or without bupivacaine was evaluated. Pertinent findings included lower delivered fraction of isoflurane necessary to maintain anesthesia and longer duration (19.6 hours) of analgesia in those patients receiving epidural analgesics[156]. Interestingly, in another study in dogs evaluating epidural morphine with or without bupivacaine, there was no difference between the group receiving morphine alone and the control group that

received a saline epidural in all investigated parameters[154]. In dogs undergoing celiotomy the effect of different epidural analgesics, intraperitoneal local analgesics and incisional (either subcutaneous or intramuscular) bupivacaine have been investigated. Results of these investigations indicate that the use of local analgesics, particularly bupivacaine, as a mode of postoperative pain management in patients following routine abdominal procedures is beneficial[40,157,158]. To the authors' knowledge, the assessment of postoperative analgesia following spinal surgery in the dog has not previously been investigated.

D. *Pain Assessment*

D1. *Subjective*

As in humans that can not self report (i.e. neonatal/pediatric, cognitively impaired adults), the ability to assess pain in veterinary patients presents inherent drawbacks and difficulties. Problems with pain assessment include the variability of the expression of pain by each patient and observer bias in evaluating patients. A published review of 27 human studies[159], demonstrated that self reports of pain are more likely to be significantly correlated with multi-dimensional behavioral ratings of pain (CPS) as compared with a single item behavioral rating (i.e. facial expression). Further, a comprehensive review of neonatal/pediatric objective pain measures concluded that multi-dimensional measures are more useful clinically and that no single domain was reliable or valid when used as a sole method[160]. Thirteen observation scales for humans with cognitive impairment were evaluated and reviewed so that conclusions could be made as to which scale is optimal[161]. These included scales based upon facial expression, pain

behavior exhibition, vocalization and the ability of nursing staff to console the patient. The authors concluded that several of the scales showed promising outcomes and motivated nurses to assess patients' pain more readily. However, varying results were found with all of the tests evaluated. The VAS is the most commonly used method for quantifying pain severity in human medicine with patients who can self-report due to its ease of use and repeatability. Though its validity in young patients where parent reporting is necessary has been questioned[162,163]. The strengths and weaknesses of the VAS have been described in several articles[164,165]. Its ease of use, good reliability and validity, and low cost are considered the benefits of the scale while the difficulty for some patients of mentally transforming a subjective sensation like pain into a mark on a straight line is considered a weakness for those who self report. In addition, the use of proxies for assessment of pain in people who can not self report are thought to be flawed by potential conceptual differences between observed assessment of pain and the self report of pain[166]. Observation of pain is generally associated with behaviors, while self reports of pain typically are associated with the perception of pain and suffering. It is thought this may be the reason why nurses and physicians underestimate their patients' pain and in some cases even think it is exaggerated[166]. When observational pain assessment is limited to a single score representing pain intensity, such as the VAS, the factors or behaviors taken into account to assign that score remain unknown. Impressions of pain intensity vary considerably among caregivers[167-170] as a result of different levels of experience with painful patients, differences in personal pain experience, or differences in the clinical background information the assessors possess[167,169]. In an effort to account for the shortcomings of each scale used separately, it is common to use multiple scales to establish a significant difference between treatment groups.

The VAS is considered to be more sensitive than simple descriptive scales or numeric rating scales in veterinary patients[171]. This method, investigated in veterinary medicine, was found to have inter-observer agreement when scoring pain and sedation[171,172]. To counter the shortcomings of the VAS, a CPS incorporating both physiologic and behavioral parameters was used in our study. The CPS in the present study [Appendix 1] was developed as an adaptation of the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) by Firth and Haldane[173] (1999). Termed the 'University Of Melbourne Pain Scale' (UMPS), this method uses multiple descriptors in six categories of data or behavior associated with response to pain.

D2. *Objective*

The ability to objectively quantify pain in veterinary patients would obviate the need for the aforementioned scales and eliminate the inherent concerns associated with their use. In 1896, von Frey first described the use of hairs of different stiffness to examine the sensitivity to touch in humans. This method was based upon the Euler buckling physical law which states that when a straight elastic fiber of constant diameter is fixed at one end and pressed with its free end vertically against the skin, the force it exerts grows until the fiber begins to bend or buckle. Once bent, the vertical force remains fairly constant even if the fiber continues to bend further. The bending force is mainly determined by the stiffness of the fiber divided by the square of its effective length. The critical force required to buckle the fiber is proportional to Young's modulus of the material and the fourth power of the diameter, and inversely proportional to the square of the length of the fiber[174]. Originally, von Frey used human hair and animal fibers with

diameters varying between 50 and 500 μm and lengths between 5 and 50 mm. These hairs were fixed to one end of a thin wooden rod at a right angle[174,175]. In the middle of the 20th century nylon replaced these hairs and sets of the Semmes-Weinstein monofilaments are still available[176]. The sets consist of 20 carrier-mounted nylon monofilaments of about 40 mm in length with diameters ranging from 0.064 mm to 1.143 mm. These filaments carry a rating number, meant to represent the 10-base logarithm of 10 times the applied force in milligrams. Typically the filaments also carry an indication of rated force (in grams)[176]. In 2001 it was suggested that the nylon fibers be replaced with optical glass fibers in order to eliminate the problems of fatigue and changes in the physical properties of nylon associated with different temperature and humidity[175,177]. In addition, there was an 8-10% variability in the diameter of nylon fibers that were produced, even from the same manufacturer[174]. In clinical work with von Frey filaments, they are applied to the patient's skin surface manually until the end point, a response from the patient, is noted.

Electronic pressure-meters are the most recent update to mechanical nociceptive testing in order to eliminate some of the disadvantages of von Frey filaments. Pressure meters are an adaptation of the classical filaments where the pressure intensity (in grams) is recorded automatically after the site of stimulation is withdrawn[178]. The von Frey anesthesiometer[k] [Figure 11] used in our study was the same model that has been established as a valid, objective, and quantitative nociceptive instrument when used to evaluate rats and mice[178,179]. Additionally, this electronic pressure-meter was found to be more sensitive than von Frey filaments when used to assess pain

in mice[179]. The von Frey anesthesiometer allows objective measurement of pain threshold that is tolerated well by canine subjects without evidence of tissue damage, learned behavior or aversion[180,181]. This model consists of a tip that is applied to the skin surface with gradually increasing force to create a noxious stimulus until a response or withdrawal is noted. The maximal force applied is automatically recorded on a monitor distant from the handpiece, so that blinded values can be obtained. It is custom adapted and successfully evaluates antinociceptive effects of morphine in dogs and has been further used for pharmacokinetic studies in this species[180,181]. Thresholds are both repeatable and consistent in dogs and allow for an objective adjunct to more subjective pain assessments (VAS, CPS).

The study described here investigated the use of epidural morphine and incisional bupivacaine for postoperative pain management in dogs following hemilaminectomy.

CHAPTER II: Evaluation of epidural morphine and incisional bupivacaine for analgesia following hemilaminectomy in the dog

A. *Objectives:*

The objective of the current study was to determine if the topical application of epidural morphine in combination with local incisional injection of bupivacaine would provide enhanced analgesia following thoracolumbar hemilaminectomy for type I IVDD in dogs. Methods used to evaluate pain included the VAS, the CPS, and von Frey thresholds. We hypothesized that the combination of epidural and local anesthetic techniques would reduce postoperative pain scores and increase cutaneous pressure thresholds following hemilaminectomy for Type I IVDD in dogs.

B. *Materials and Methods:*

Animals

Patients selected for inclusion in the study were otherwise healthy dogs presented to the Veterinary Teaching Hospital with suspected thoracolumbar, Hansen type I IVDD confirmed at surgery. Inclusion criteria required that each dog have deep pain perception at the time of the initial neurologic exam, and weighed <15 kg. Patients with multiple thoracolumbar sites that required surgery and those that had previous hemilaminectomy surgery at a distant site remained in the study. Aggressive behavior, and/or any patient who progressed to negative sensory status during the 48 hour study period were removed from the study. Fenestration of the disk at the site of the hemilaminectomy was permitted per surgeon preference. However, fenestration of disks at adjacent sites disqualified the patient from the study. In all cases, informed consent was

obtained from the owners. The study design was approved by the Institutional Animal Care and Use Committee.

Study Design

Each dog was randomly assigned to one of the four treatment groups [Table 1] upon acceptance into the study. Assessment for deep pain sensation was completed by one of the investigators (FBH)[a] at the time of presentation to the clinic, prior to administration of any parenteral opioids including those used for premedication.

Anesthesia and Surgery

A standardized pre-medication protocol consisting of either midazolam[b] or diazepam[c] at a dose of 0.1 – 0.5 mg/kg intramuscularly (IM) and morphine[d] at a dose of 0.5 – 1.0 mg/kg IM was given prior to induction of general anesthesia. Premedications were administered at sites distant from the expected dorsal midline region of the surgical incision. Propofol (PropoFlo™)[e] was titrated intravenously for anesthetic induction (up to 6 mg/kg) and anesthesia was maintained with isoflurane[f] in oxygen. Intravenous (IV) fluids were administered at l0 ml/kg/hr and ventilation was assisted or controlled to maintain end tidal carbon dioxide concentrations between 35-45 mmHg. Body temperature was monitored with an esophageal probe and maintained between 37-39°C with either a circulating warm water or forced air blanket. The ECG, heart rate, and oxygen saturation were monitored throughout the anesthetic period. Once the patients were anesthetized, computed tomography (CT) or myelography was performed preoperatively to determine the site of the disk extrusion. Hemilaminectomy was performed on all dogs by a dorsal midline incision or slightly paramedian incision, and muscle dissection on

the appropriate side by a resident, ACVS board-certified surgeon, or ACVIM board-certified neurologist. Hansen type I disk extrusion was confirmed during the surgical procedure.

Following hemilaminectomy and disk removal and prior to closure of the surgical site, dogs in the DUR/SAL and DUR/BUP groups received 0.1 mg/kg (1.0 ml/10 kg of body weight) of preservative free morphine sulfate (Duramorph™)[g] epidurally. The Duramorph™ was administered topically by an 18 gauge intravenous catheter (Jelco®)[h] placed into the epidural space through the hemilaminectomy site. The catheter was marked with a sterile marker so that it was advanced 2 cm cranially in the epidural space from the most rostral aspect of the hemilaminectomy site. Dogs in the SAL/SAL and SAL/BUP groups received an equal volume of saline epidurally, administered in a similar manner. Absorbable gelatin compressed sponge (Gelfoam®)[i] cut to the size of the hemilaminectomy, was placed over the hemilaminectomy site once the epidural injection was complete. No further lavage or suction was performed. The lumbar fascia and muscle were routinely closed in all dogs. All dogs in the DUR/BUP and SAL/BUP groups received 2.0 mg/kg of 0.25% bupivacaine (8.0 ml/10kg of body weight). The bupivacaine was injected into the paraspinal musculature along a one centimeter margin of the muscular incision with a 22-gauge needle. Equal aliquots were deposited on each side of the incision. Dogs in the SAL/SAL and DUR/SAL groups received an equal volume of saline administered in the same manner. All other intraoperative analgesic administration was at the discretion of the attending anesthesiologist. The subcutaneous and intradermal tissues were then closed in a routine manner. The skin was closed with skin staples. All non-ambulatory dogs had closed system urinary catheters placed postoperatively which were maintained for a minimum of 48 hours.

All investigators, students and staff were blinded to the contents of the vials containing drugs or saline. All staff involved in the study received further instruction not to break blinding if they were to become personally aware of what drug was in a particular bottle due to inherent differences between the pharmaceutical substances (i.e. scent, viscosity, color).

A mark was placed on each patient at 1 cm and 3 cm lateral to the midpoint of the incision on the side of the incision that the hemilaminectomy was performed. Further, a box was drawn outlining the perimeter of the study area isolating the incision so that no other IM or subcutaneous (SC) injections were given near the testing site [Figure 12]. Jugular catheters were also placed in all dogs so that blood samples could be obtained at each assessment. The intended use of the blood samples was to quantify blood glucose and cortisol levels at the conclusion of the study. (This analysis was not pursued.) Anesthesia was discontinued after all surgical procedures were completed and the dogs recovered and remained housed for the duration of the study period in a designated isolated area of the intensive care unit.

All dogs received a 0.25 mg / kg dose of morphine IM at extubation. They also received additional doses of morphine SC at a dose of 0.5mg/kg every 4 hours for 48 hours following surgery. All postoperative morphine injections were given outside of the previously designated area [Figure 12].

Drugs used for both the epidural and local incisional injection were stored in a locked box and labeled with the letters A - D. All vials were labeled as "Duramorph™" or "bupivacaine" even if

the vial contained saline, and all removed narcotic labeled drugs were recorded as required in a controlled drug log. The Veterinary Teaching Hospital pharmacy maintained record of the bottles and what drug was in each (or if it was saline) and which letter (A-D) corresponded with which treatment group. There were two sets of bottles for each group in the event that there was inadvertent contamination or breakage of the bottle.

Pain and Sedation Assessment

Pain assessment was completed by the same investigator (FBH) for the duration of the study period. The visual analog score (VAS) for pain, as used in the present study, consisted of a 100 mm line on a piece of paper with the extent of the limits marked as no pain (left extent) and severe pain (right extent). A mark was placed on the line by the observer (FBH) as a representation of the perceived level of pain and the length (mm) as measured from the left extent of the line was the score assigned[182-184]. The VAS sedation score was performed in the same manner, with the left extent marked as completely alert and the right extent marked as unconscious. In addition to the VAS a composite pain scale (CPS) that incorporated both physiologic and behavioral parameters was also used [Appendix 1]. Throughout the study period, if the VAS pain score was >50 and/or the CPS score was >14, at any given assessment interval, a morphine dose was given for breakthrough pain at a dose of 0.25 mg/kg SC. This breakthrough dose was recorded on the patient record. If sedation was necessary or if the patient was dysphoric (particularly at extubation), acepromazine maleate[j] at a dose of 0.02 mg/kg IV was given following assessment by the same investigator (FBH).

Assessment of postoperative pain levels was performed by one blinded investigator (FBH). This included the application of the VAS pain, CPS, VAS sedation and cutaneous pressure response threshold using a von Frey anesthesiometer[k] [Figure 11]. Patient pain assessment occurred at 0.5, 2, 4, 8, 12, 18, 24, 36 and 48 hours post extubation. Dogs were first observed for one minute, undisturbed, from outside of the kennel. Respiratory rate and activity were recorded. The observer then approached the dog's kennel with a standard greeting used for all dogs. The dog's behavior in response to the observer was recorded and heart rate determined. Response to cutaneous pressure 1 cm and 3 cm from the incision site [Figure 12] was then evaluated using the von Frey anesthesiometer. Three repeated measurements were performed at each site. The assessor was blinded to the pressure readings as the handpiece for the device is located distant from the recording device. This allowed maximal pressure readings to be recorded by the anesthesiometer and evaluated by FBH following collection of the data. Additionally, the left or right lateral stifle was also assessed for a response using the von Frey anesthesiometer. This was also repeated three times. A time of one minute was allowed to elapse between each of the measurements and each site was measured on a rotating basis (i.e. 1 cm mark followed by the 3 cm mark followed by the stifle, then repeat). Pain scores from the VAS and CPS, VAS sedation, von Frey pressure at both 1 cm and 3 cm, von Frey pressure at the stifle, and number of breakthrough morphine doses were recorded.

Data Analysis

Outcomes evaluated statistically included CPS, VAS for both pain and sedation, and von Frey pressure thresholds at both 1 cm and 3 cm from the incision (VF1 and VF3, respectively) and the lateral stifle. A logarithmic (base e) transformation was applied to the VAS to obtain an

approximate Gaussian distribution. For each outcome, significant differences between treatment groups ($p < 0.05$) at each interval and as well as over the entire 48-hour period were investigated using repeated measures ANOVA. To adjust for multiple comparisons, Tukey's procedure was applied. The effect of surgeon was also investigated separately in a secondary analysis using mixed-model repeated measures analysis of variance. After initial data requisition and assessment, the two treatment groups that received epidural Duramorph™ were compared to the two groups that did not receive the epidural Duramorph™ using contrasts. For each analysis, model adequacy was evaluated using residual plots. Statistical significance was set to $\alpha=0.05$. All data analyses were performed using SAS® 9.2 (Cary, NC, USA)[1].

C. *Results:*

Demographic Data

There were 16 female and 17 male dogs. The dogs were randomly distributed among treatment groups as follows: 9 dogs in SAL/SAL, 8 dogs in BUP/SAL, 8 dogs in DUR/SAL, and 8 dogs in DUR/BUP for a total of 33 dogs. There were 27 dachshunds and 6 other breeds. Those dogs that were breeds other than dachshunds included 1 Pekingese, 1 Lhasa Apso, 2 Beagles, and 2 mix breed dogs. They were distributed between treatment groups as follows: 2 in DUR/BUP, 2 in DUR/SAL, 1 in SAL/SAL and 1 in SAL/BUP. The average weight of all the dogs was 7.75 kg (range 4.5 – 15.0 kg) and the average age was 6.5 yrs. (range 3 – 13 yrs.).

Diagnostics

Four dogs had a myelogram performed prior to surgery, one of whom also had a CT. Of these dogs 2 were in the SAL/SAL group, 1 was in the DUR/BUP group, and the one that had both diagnostics performed was in the SAL/BUP group.

Surgery

Surgery was performed by eight people including 2 surgical residents, 1 neurology resident, 3 ACVS Diplomates and 2 ACVIM (Neurology) Diplomates. Residents performed surgery on 22 dogs, 11 of the dogs had surgery performed by Diplomates (ACVS or ACVIM [Neurology]). The average length of surgery was 1.6 hours (range 0.5 – 4.25 h). Six dogs had a hemilaminectomy performed at more than one intervertebral disk space. These six dogs were distributed between all four treatment groups as follows: 2 DUR/BUP, 2 SAL/SAL, 1 SAL/BUP, and 1 DUR/SAL. None of the dogs had prior hemilaminectomy for intervertebral disk disease.

CPS

Composite pain scoring was performed using a previously established set of criteria [Appendix 1]. The maximum score possible using the CPS was 24 and the minimum was zero. Over the 48-hour study period, there was a significant difference between DUR/BUP (mean 6.9, range 2 to 14) and both SAL/SAL (mean 4.8, range 0 to 12) ($p = 0.049$) and SAL/BUP (mean 4.5, range 0 to 13) ($p = 0.012$), however there was no difference when each interval was investigated separately [Figure 13].

VAS Pain

Scores were not significantly different between any of the groups at any time interval throughout the study [Figure 14].

VAS Sedation

Sedation scores were not significantly different between any of the groups at any time interval throughout the study [Figure 15].

VF 1 cm Threshold

At the 2 hour ($p=0.0046$), 8 hour ($p<0.0001$), 12 hour ($p<0.0002$) and 18 hour ($p<0.0001$) intervals, the VF 1 cm threshold was significantly different between groups [Table 2, Figure 16]. However, at no interval was there a difference between DUR/SAL and DUR/BUP or SAL/SAL and SAL/BUP. In summary, the incisional bupivacaine alone did not have an effect on von Frey thresholds.

Moreover, at the 2 hour ($p=0.0084$), 4 hour ($p<0.0001$), 8 hour ($p<0.0001$), 12 hour ($p=0.0002$), 18 hour ($p<0.0001$) and 24 hour ($p<0.0001$) intervals, the groups receiving the epidural Duramorph™ (DUR/SAL and DUR/BUP) had significantly lower thresholds than the other two groups (SAL/SAL and SAL/BUP).

VF 3 cm Threshold

Significant differences between groups were noted at the 0.5 hour (p=0.0414), 2 hour (p=0.0345), 8 hour (p=0.0126), 12 hour (p=0.0348), 18 hour (p=0.0017), and 24-hour interval (p=0.0003) [Table 3, Figure 17]. However, the statistical significance disappeared after correcting for multiple comparisons. When the groups were assessed over the entire study period (0.5-48 hours) the DUR/SAL group had lower thresholds than either SAL/SAL (p=0.029) or SAL/BUP (p=0.0018) [Table 2, Table 3]. Furthermore, DUR/BUP also had lower thresholds than either SAL/SAL (p=0.0262) or SAL/BUP (p=0.0015) [Table 2, Table 3]. When the groups that received Duramorph epidurally were combined and compared to those that did not, no significant difference was found.

VF Stifle

There was a significant difference between the DUR/SAL (mean 720.0, range 563.3 to 851.5) and DUR/BUP (mean 844.8, range 802.5 to 875.1) groups at the 18 hour interval (p=0.0415) and when comparing these two groups over the entire study period (p=0.0270). Once those groups receiving the epidural Duramorph™ were combined and compared to those that did not, there was no significant difference noted.

Breakthrough Morphine Requirements

Eleven dogs required a dose of morphine for breakthrough pain within the first 4 hours of the study period. None of these dogs were in the SAL/BUP group. Three of the dogs were in the SAL/SAL group and there were four in each of the DUR/SAL and DUR/BUP groups. The total number of breakthrough doses was 12, 75% (9/12) were given to those dogs in the DUR/SAL and DUR/BUP groups. Eight dogs had to have their postoperative morphine dose decreased or

were removed from the study completely due to intractable side effects associated with morphine administration. These side effects included nausea (hypersalivation, eructation, excessive lip licking), regurgitation, persistent hypothermia, and bradycardia. Both of the dogs that were able to tolerate a lower dose of morphine without having to be discontinued and therefore removed from the study were in the SAL/SAL group. Overall, 6 dogs were removed from the study early. Three dogs in the DUR/BUP group, 2 dogs in SAL/BUP group, and 1 in the DUR/SAL group. Cessation of morphine treatment occurred at the 24 hour interval for one dog, the other 5 dogs were discontinued at the 36 hour interval. All data collected prior to removal of the study was included for statistical analysis. None of these dogs were in SAL/SAL and 66% (4/6) were in those groups that received the epidural Duramorph™. Two of the eleven dogs that received a breakthrough dose of morphine were also within the group of 6 dogs that were removed from the study early.

Surgeon

There was no effect of surgeon on any variable at any time interval throughout the study period.

D. *Discussion:*

The results of this study did not substantiate our hypothesis. The dogs receiving epidural Duramorph™ applied to the spinal cord and/or incisional intramuscular injection of bupivacaine following hemilaminectomy did not have lower postoperative pain scores and higher cutaneous pain thresholds than those dogs treated with parenteral morphine administration alone.

On the contrary, those dogs treated with epidural Duramorph™ exhibited significantly lower pain thresholds than those that did not receive the epidural narcotic. Additionally, the administration of bupivacaine injected intramuscularly around the incision prior to closure of the skin was not found to contribute significantly to post-operative pain control.

The use of more than one pain assessment system, including the VAS and CPS attempted not only to compensate for the short comings of each assessment alone, but also to correlate these more subjective assessments with an objective measurement of pain threshold. Indeed, the VAS and CPS findings correlated with those of the von Frey thresholds when the data was evaluated over the entire study period (48 hours) with those groups receiving epidural Duramorph™ scoring higher on both the VAS and CPS and having significantly lower von Frey thresholds. However, the VAS and CPS appeared less sensitive in that significantly different measurements evaluated at each assessment interval separately did not correlate with and were fewer in number than differences between groups found with von Frey threshold. Unfortunately, it was clear during the study that several of the dogs developed aversion to the von Frey anesthesiometer. Due to jugular catheter placement, it was not possible for the dogs to wear Elizabethan collars which might have prevented them from visualizing the probe. Aversion was characterized by aggressive behavior as the handpiece was approaching the dog before the probe made contact with the skin. In most cases, covering the head with a blanket and repeating the assessments allowed completion of data collection. This may differ from Kukanich's findings because in those investigations[180,181] the von Frey anesthesiometer was used in non-painful dogs by applying the probe to their paw pads.

A low concentration (0.25%) of bupivacaine was used so that a relatively large volume of anesthetic fluid could be distributed evenly into the muscle around the incision. In addition, instructions were given to the surgeon to administer the injection 1 cm away from the incision in the paraspinal musculature, using a 22- gauge needle, as equal, separate aliquots along the length of the entire incision line. Contrary to previous studies in animals that received incisional bupivacaine following celiotomy, the addition of incisional bupivacaine in the present study population did not enhance analgesia following surgery. This may be due in part to the difference in the severity, combination, and duration of pain experienced by patients with intervertebral disk disease and hemilaminectomy as compared to otherwise healthy dogs that have an elective orthopedic or abdominal procedure performed. The major mechanism of action of local anesthetics is the stabilization of peripheral nerve membranes. Additionally, local anesthetics affect many membrane-associated proteins in tissue and can inhibit the release and action of agents like prostaglandins and lysosomal enzymes, which sensitize or stimulate nociceptors and promote inflammation[128]. In the previous studies bupivacaine was evaluated as pre-emptive analgesia for elective procedures with the drug administration occurring prior to the incision, rather than at the end of the procedure just prior to closing the skin[132,185]. In the present study, the lack of benefit noted from the bupivacaine may be attributed to a combination of the aforementioned limitations. In addition, though measures were taken to ensure that the bupivacaine was administered in a consistent manner around the incision, it is possible that there was some variability. In some cases, the bupivacaine was diluted with saline prior to injection so that a subjectively adequate volume was obtained prior to administering the drug. The depth of

administration into the musculature was also not controlled. These factors may also have contributed to the present findings.

Epidural and local analgesia have been investigated in veterinary patients undergoing various surgical procedures including fracture repair, tibial plateau leveling osteotomy (TPLO), ovariohysterectomy (OHE), celiotomy for procedures other than OHE, and total ear canal ablation (TECA)[40,153-158]. However, these studies were evaluating the effects of these drugs primarily as pre-emptive analgesics. The study that evaluated postoperative TECA dogs did not find a difference between dogs that received bupivacaine locally and those that did not. All of the dogs in that study were also receiving parenteral morphine so it was impossible to determine if a benefit would have been recognized in the absence of those additional narcotics or a lower dose. In a study that evaluated 265 cases[156], a higher epidural morphine dose was used (0.2 mg/kg) as compared to the present study (0.1 mg/kg). Perhaps the dosage chosen for the present study was too low for a significant benefit to be determined. Another possible contribution to our findings was the method chosen for administration of the epidural. The drug was administered via a catheter within the spinal canal and administered in a cranial direction from the hemilaminectomy site. Due to spinal blood flow and the flow of CSF, this may have been an inappropriate method to achieve analgesia along the entire spinal cord as it is unlikely to then flow in a caudal direction. The Duramorph™ may have been better administered infused into the Gelfoam® so that less dilution by blood and tissue fluids occurred, loss into the disk space was avoided, and more prolonged, controlled absorption was achieved[37]. Another consideration was that myelography had caused irritation of the meninges and possibly contributed to increased

pain in select groups. However, there were only 4 patients that had a myelogram performed and only 1 of the 4 was in a group that received epidural Duramorph™.

The potential detriment (evidenced by lower von Frey pain thresholds) to patients that were administered Duramorph™ epidurally was more difficult to explain and was an unexpected and interesting outcome of the study. Acute opioid tolerance has been investigated and described in both animal and human studies[186,187]. The basis of this concept is that patients can develop a diminished response to subsequent doses after being administered opioid medication during anesthesia, and actually require higher or more frequent dosages in the post-operative period. Of note in the present study is the finding that 66% of those dogs requiring breakthrough doses of morphine were in the groups given the epidural Duramorph™. In addition, 75% of the breakthrough doses administered over the entire study period were given to dogs in those groups. The development of acute tolerance to narcotics was first described in the early 1930's[188]. Investigations were carried out in animal subjects in order to determine the mechanism for the tolerance developed by people given chronic narcotic therapy. It was found that this tolerance can develop after very short term use, in some cases, only one dose, and termed it acute tolerance[187,189-192]. Since that time, numerous and varied studies have attempted to elucidate the cellular and neuronal mechanism for this type of response, and for the most part, it remains unknown[186,193,194]. Compelling evidence indicates that activation of spinal cord N-methyl-D-aspartate (NMDA) receptors contribute to the hyperalgesia that occurs following peripheral nerve injury or inflammation[195-201]. Several studies have evaluated the use of NMDA receptor antagonists (intrathecally or intraperitoneally) following peripheral nerve injury and conclude

that there is a significant reduction in thermal hyperalgesia in animal models of neuropathic pain[186,197,202-205]. In addition, electrophysiological techniques also have demonstrated the NMDA mediated enhancement of spinothalamic neuron responses to mechanical, thermal, and electrical stimuli[196]. These data strongly indicate that spinal cord activation of the NMDA receptor in response to peripheral tissue injury and inflammation is critical both for the development and maintenance of hyperalgesia. Likewise, the activation of NMDA receptors within the spinal cord plays a crucial role in the development of tolerance to the analgesic effects of morphine[186,199,206,207]. It is further suggested that the same spinal cord neurons are involved in the neural mechanisms of both hyperalgesia and morphine tolerance[130,208] and that there is a predictable interaction between intracellular mechanisms and the development of these two states. Neurochemical events associated with hyperalgesia would therefore lead to decreased analgesic effects of morphine[186,208-211]. The development of tolerance may be exacerbated following morphine treatment or reduced morphine antinociception may occur prior to the first exposure to the drug[187,201,211-213].

Studies have also indicated a reduction in morphine antinociception under conditions of wind up or central sensitization[123,201,211,214-217]. The clinical implication of this work remains controversial. It is conceivable that the diversity of clinical response patterns to opioid treatment in neuropathic pain patients may result from varying degrees of neuronal changes initiated by nerve injury. These neuronal changes may underlie the development of neuropathic pain syndromes and result in reduced morphine analgesia even before opioid treatment is initiated. To complicate this scenario further, neuropathic pain syndromes often present a dynamic and

progressive course that demands increased opioid doses for increased pain relief. The complexity of opioid tolerance, tolerance associated hyperalgesia, and the progression of the original pathologic disorder, make it increasingly difficult to determine whether different response patterns to opioid treatment in subjects with neuropathic pain results from one or all of these factors.

In theory, the administration of morphine topically as an epidural in patients of the present study lead to an overall increase in the opioid that accumulated in dorsal root ganglia during anesthesia[218]. This potentially contributed to acute tolerance in the post-operative period[219], thereby causing decreased pain thresholds and an increased requirement for analgesics in dogs of those treatment groups. This could be attributed to the local inflammation and permeability changes[220] in the region associated with not only the initial injury (disk herniation) but also the surgical procedure itself. It may be inappropriate to compare analgesic outcomes of dogs with spinal injury and spinal surgery with those that are receiving an epidural prior to surgery for extra-spinal elective procedures as in other studies. Further, conclusions about epidural administration in these patients should not be drawn from prior studies. More work is needed in the assessment of neuropathic surgical pain in veterinary patients to establish the most efficacious analgesic regimen.

Due to the nature of this clinical study, several surgeons with varying levels of expertise were involved. This included Diplomates (ACVS, ACVIM [Neurology]) and residents. Attempts were made to ensure that cases were equally distributed between residents and Diplomates and

within treatment groups. The effect of surgeon experience was not found to be statistically significant. In addition, the authors believe this situation is most representative of how these cases are managed at most academic institutions, so the findings are applicable and representative.

E. *Conclusion:*

The combination of epidural Duramorph™ and incisional bupivacaine in the present study did not reduce pain scores or increase cutaneous pressure thresholds following hemilaminectomy for Hansen type I IVDD in dogs. Based on the results of this study, and determination of higher pain scores with lower thresholds, we do not recommend the use of topically administered epidural morphine (Duramorph™) for analgesia in patients undergoing thoracolumbar hemilaminectomy for Hansen Type I IVDD. Further, there was an absence of significant benefit to reduction in pain scores or cutaneous pressure thresholds with the administration of bupivacaine intramuscularly around the incision alone.

F. *Footnotes:*

a) Farrah B. Horowitz, DVM

Virginia-Maryland Regional College of Veterinary Medicine

Virginia Tech

Department of Small Animal Clinical Sciences

b) Midazolam

Spectrum Chemical Mfg. Corp.

14422 South San Pedro Street

Gardena, California 90248, USA

c) Diazepam

Hospira, Inc.

Lake Forest, IL 60045 USA

d) Morphine sulfate

Hospira, Inc.

Lake Forest, IL 60045 USA

e) PropoFlo™ABBOTT

Abbott Animal Health

200 Abbott Park Road

Abbott Park, IL, 60064-6375

f) Isoflurane

Hospira, Inc.

Lake Forest, IL 60045 USA

g) Duramorph is a trademark of Baxter International, Inc., or its subsidiaries.

Baxter Healthcare Corporation

Deerfield, IL 60015 USA

h) Jelco®

Smiths Medical

Smiths Group plc:

Registered office 765 Finchley Road, London NW11 8DS

Incorporated in England No. 137013

i) Gelfoam®

Pfizer Inc.

Pharmacia & Upjohn Company

235 East 42nd Street

New York, NY 10017 USA

j) Acepromazine Maleate

Boehringer Ingelheim Vetmedica, INC.

2621 North Belt Highway

St. Joseph, MO, 64506-2002

k) von Frey Anesthesiometer

IITC Life Science Inc.

23924 Victory Blvd Woodland Hills, CA 91367

l) SAS® 9.2

SAS Worldwide Headquarters

Cary, North Carolina

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APPENDIX I: Figures

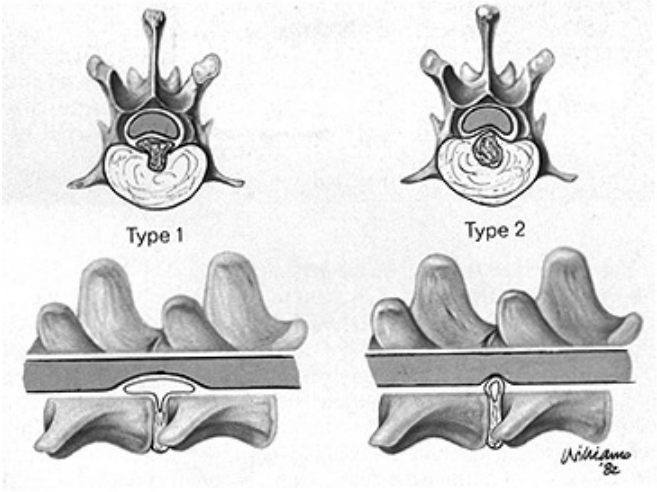

Figure 1 – Image describing Hansen type I disk extrusion and Hansen type II disk extrusion. The top images are of a transverse section through the intervertebral disk space. The bottom images are a sagittal section through the midline of the vertebral canal over the site of disk injury. (From *Intervertebral Disc Disease* by Toombs JP, Waters DJ, in Textbook of Small Animal Surgery, 2002 Saunders, pg. 1995)

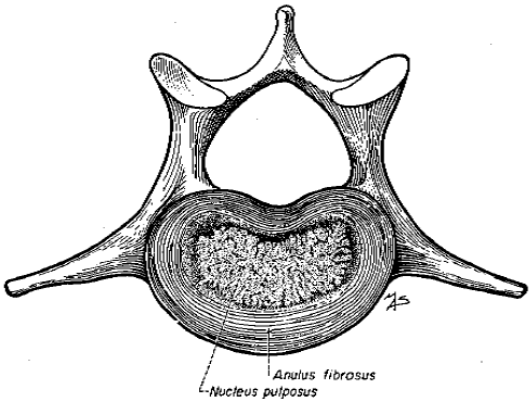

Figure 2 – Lumbar vertebra showing the intervertebral disk. Note the outer annulus fibrosus and the inner nucleus pulposus. (From *Miller's Anatomy of the Dog* by Evans HE, 3rd ed., pg. 230)

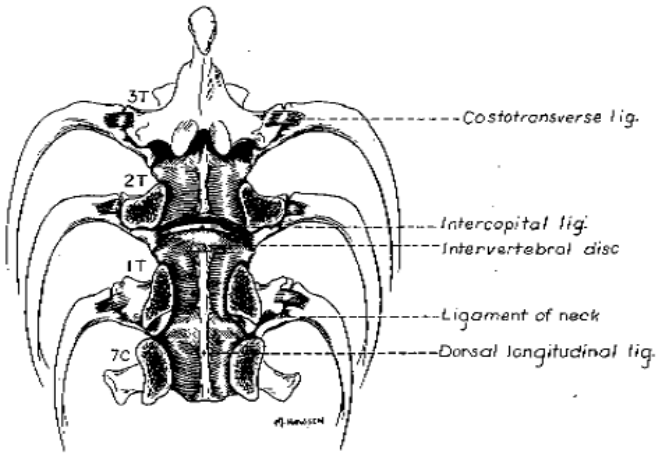

Figure 3 – Image of the supporting structures around the thoracic vertebra. Note the relationship between the intercapital ligament and the intervertebral disk. (From *Miller's Anatomy of the Dog* by Evans HE, 3rd ed., pg. 231)

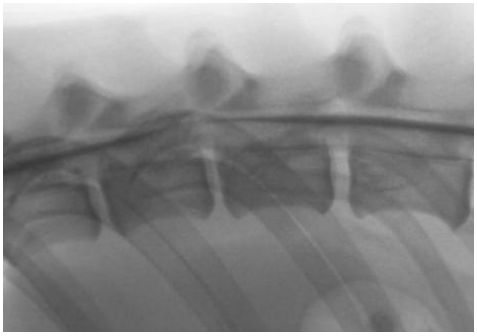

Figure 4 – Lateral fluoroscopic myelogram showing extradural compression of the spinal cord at the T12-T13 disk space. Note the absence of contrast ventrally and thinning of the contrast column dorsally.

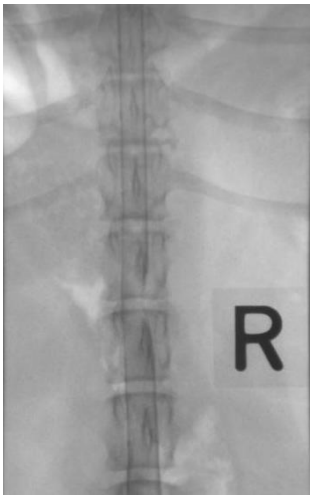

Figure 5 – Dorsoventral fluoroscopic myelogram showing extradural compression of the spinal cord at the L1-L2 disk space on the right side.

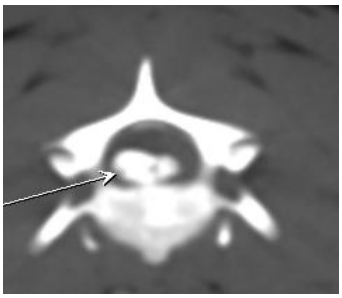

Figure 6 – Transverse CT image of a lumbar intervertebral disk space. Note the mineralized mass [arrow] within the ventral aspect of the canal (consistent with disk material).

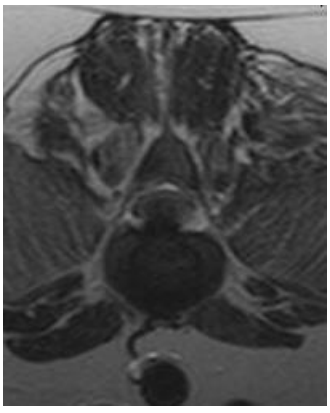

Figure 7 – Transverse t2-weighted MRI image of a lumbar intervertebral disk space. Note the low signal intensity mass compressing the ventral spinal cord.

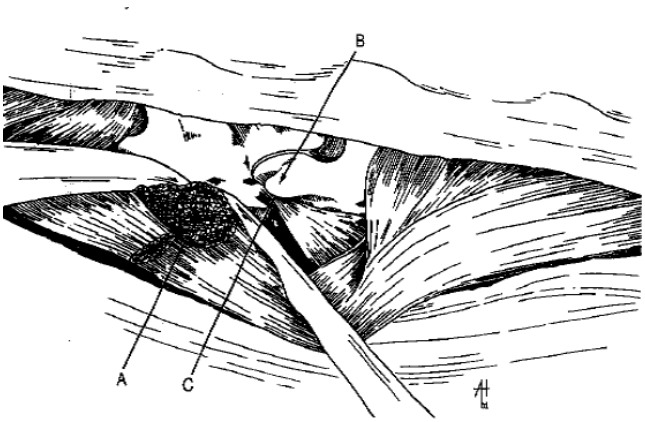

Figure 8 – Dorsolateral approach to the thoracolumbar spine. (A) Multifidus Muscle, (B) Mammilary Process, (C) Intervertebral disk space. (From *Surgical Approaches to the Central Nervous System, Spine.* By Coates JR, Hoffman AG, Dewey CW In Slatter: Textbook of Small Animal Surgery, pg. 1158.)

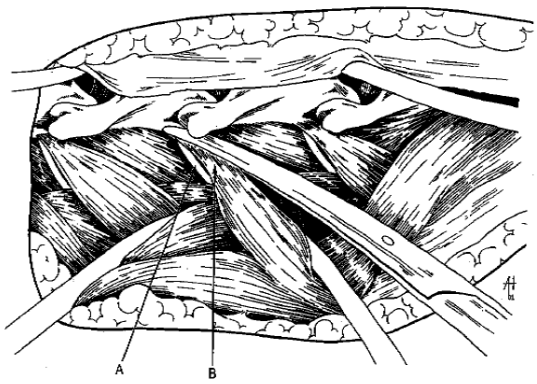

Figure 9 – Dorsolateral approach to the thoracolumbar spine continued from Figure 12. (A) Spinal nerve root, (B) Insertion of the longissimus muscle on the accessory process. (From *Surgical Approaches to the Central Nervous System, Spin.* By Coates JR, Hoffman AG, Dewey CW in Slatter: Textbook of Small Animal Surgery, pg. 1158.)

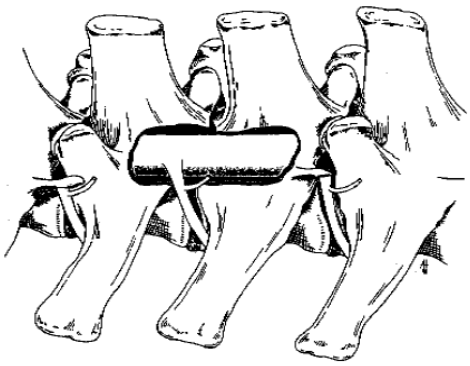

Figure 10 – Depiction of a completed hemilaminectomy. (From *Myelopathies: Disorders of the Spinal Cord*, by Dewey CW in A Practical Guide to Canine and Feline Neurology, pg. 335.)

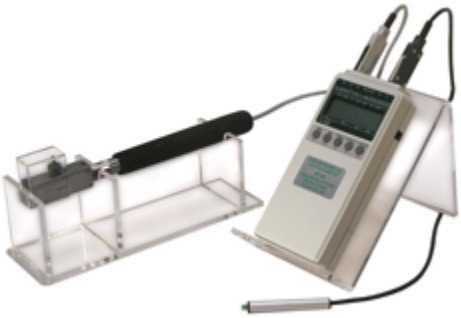

Figure 11 – Photo of von Frey Anesthesiometer. (From www.iitcinc.com)

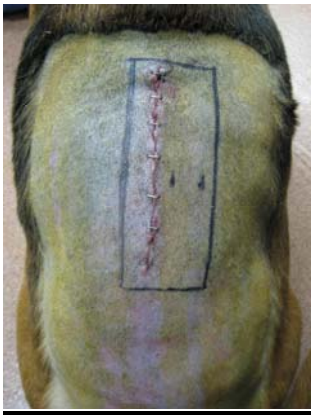

Figure 12 – Postoperative right sided hemilaminectomy study dog photo showing test site marking described for obtaining von Frey thresholds. Note the individual markings on the right side of the incision indicating 1 cm and 3 cm lateral to the midpoint of the incision line. In addition, there is a box around the incision delineating acceptable areas for any necessary subcutaneous or intramuscular injections.

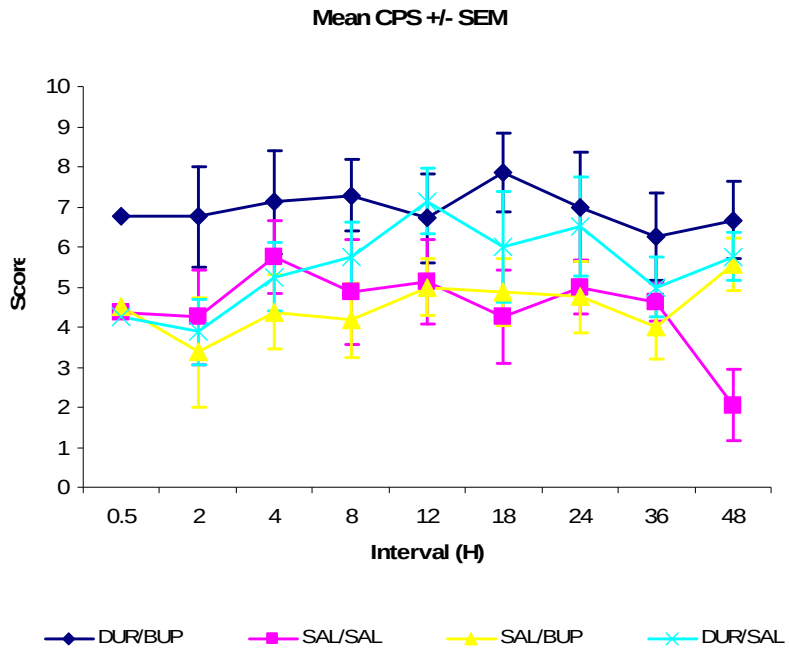

Figure 13 – Graphical depiction of the mean CPS scores for each interval +/- SEM.

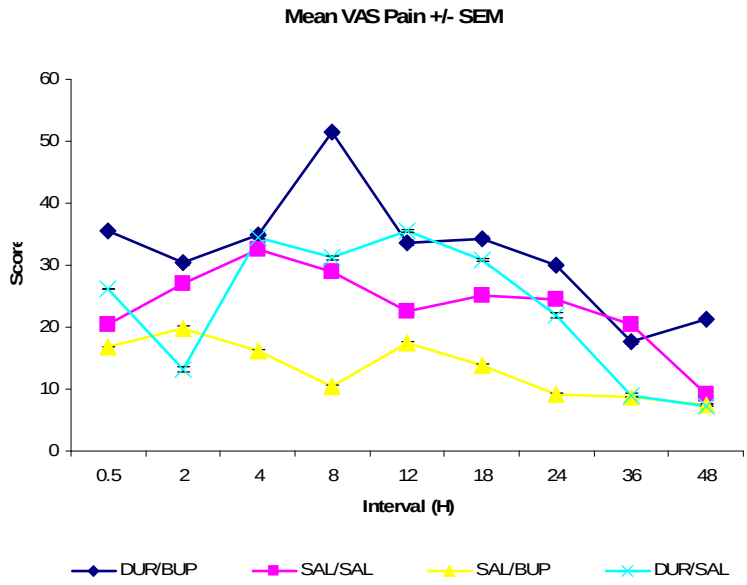

Figure 14 – Graphical depiction of the mean VAS pain scores for each interval +/- SEM.

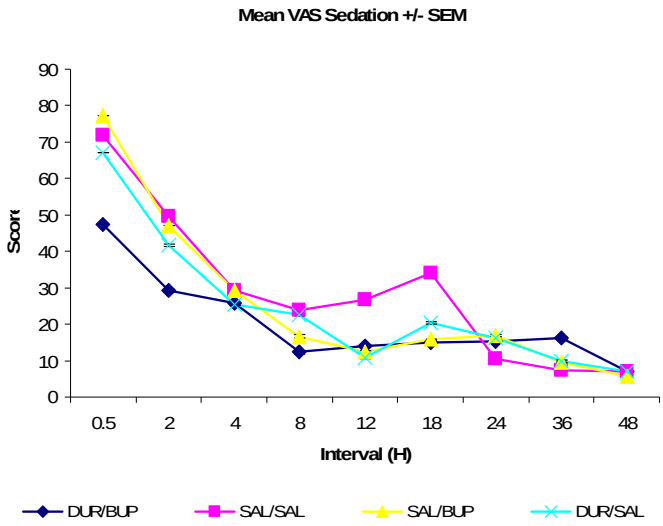

Figure 15 – Graphical depiction of the mean VAS sedation scores for each interval +/- SEM.

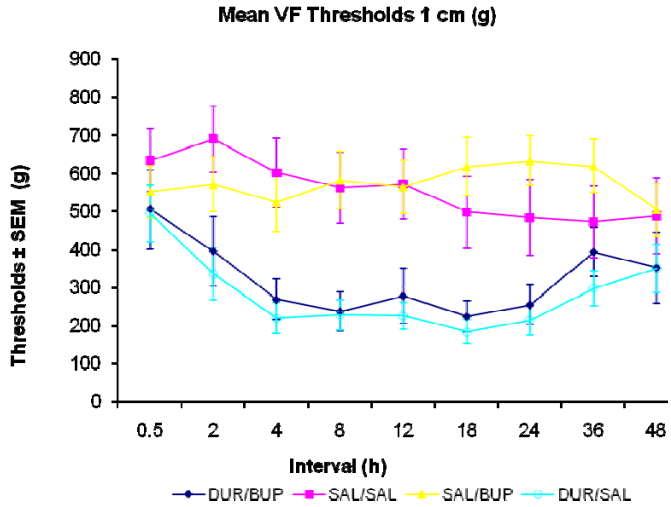

Figure 16 – Graphical depiction of Von Frey thresholds (g) obtained at 1 cm from the surgical incision at each interval.

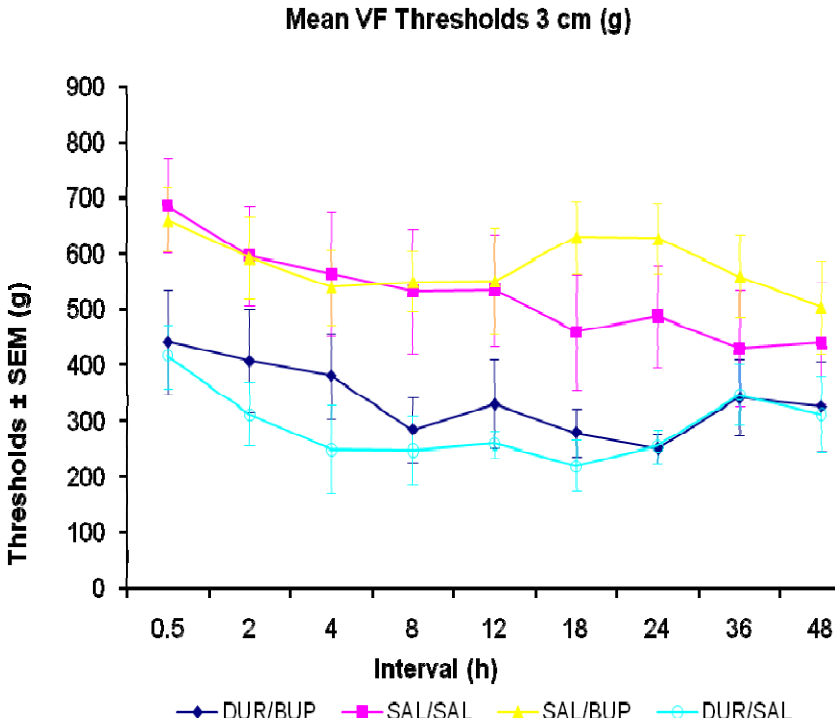

Figure 17 – Graphical depiction of Von Frey thresholds (g) obtained at 3 cm from the surgical incision at each interval.

APPENDIX II: Tables

Table 1. Study Groups

Group	Treatment
DUR/BUP	Duramorph™ epidural/incisional intramuscular bupivacaine
DUR/SAL	Duramorph™ epidural/incisional intramuscular saline
SAL/BUP	Saline epidural/incisional intramuscular bupivacaine
SAL/SAL	Saline epidural/incisional intramuscular saline

Table 2. Mean VF 1 CM (g)*

Interval	DUR/BUP	DUR/SAL	SAL/BUP	SAL/SAL	P-VALUE†
0.5	504.76 (144.4-897.0)	494.44 (155.5-748.0)	550.7 (259.9-791.6)	634.5 (216.9-959.4)	0.5997
2	395.3 (76.4-845.2) [a]	335.36 (154.6-671.7) [b]	569.7 (226.1-771.2)	689.6 (285.3-1026.5) [a, b]	0.0046
4	268.6 (97.8-530.4) [a]	220.35 (63.3-380.1) [b, c]	523.1 (211.5-768.2) [c]	601.5 (184.6-983.7) [a, b]	0.0008
8	237.6 (68.2-443.7) [a, b]	228.2 (82.5-385.5) [c, d]	582.1 (265.5-807.0) [b, d]	562.1 (74.6-917.2) [a, c]	<0.0001
12	277.8 (49.3-551.0) [a, b]	226.6 (132.9-381.9) [c, d]	564.4 (166.5-753.1) [b, d]	571.4 (155.7-991.2) [a, c]	0.0002
18	224.7 (90.0-342.9) [a, b]	184.3 (76.1-313.7) [c, d]	617.2 (284.8-826.1) [b, d]	497.8 (191.3-891.5) [a, c]	<0.0001
24	254.9 (127.2-525.2) [a]	214.7 (43.8-380.4) [b, c]	633.2 (351.9-848.6) [a, c]	483.0 (39.8-976.3) [b]	0.0007
36	393.1 (177.7-743.2)	297.75 (112.6-473.1) [a]	618.91 (301.5-792.2) [a]	472.7 (121.8-937.1)	0.0317
48	351.7 (143.3-748.1)	350.3 (104.1-606.1)	503.8 (266.9-746.6)	488.41 (154.1-951.5)	0.4168
0.5-48	325.2 (35.1-897)	283.5 (43.8 – 748) [a, b]	573.7 (166.5 - 848.6) [b]	555.7 (39.8 –1026.5) [a]	0.0015

*Numbers are means (range).
†P-values for comparing groups within interval.
[a,b,c,d] Groups with the same letter are significantly different after Tukey's procedure for multiple comparisons.

Table 3. Mean VF 3 CM (g)*

Interval	DUR/BUP	DUR/SAL	SAL/BUP	SAL/SAL	P-VALUE†
0.5	441.3 (156.3 – 860.3)	415.5 (249.4-634.9)	660.0 (449.0-871.0)	685.5 (208.5-1015.9)	0.0414
2	406.3 (103.9-761.1)	310.8 (160.9-652.7)	592.2 (184.7-788.3)	595.8 (185.7-921.4)	0.0345
4	379.4 (74.9-775.9)	247.8 (50.5-724.5)	539.1 (227.5-773.5)	564.0 (30.7-1064.0)	0.0530
8	283.5 (85.5-521.6)	246.5 (31.2-530.2)	549.0 (409.6-723.8)	531.4 (5.4-961.8)	0.0126
12	329.4 (87.1-600.1)	257.4 (177.9-373.7)	550.7 (21.7-757.6)	533.9 (155.3-942.5)	0.0348
18	278.0 (76.0-419.9)	219.4 (81.2-463.0)	629.6 (338.2-845.9)	459.2 (97.2-900.4)	0.0017
24	248.6 (161.6-342.7)	253.6 (131.5-412.4)	626.7 (381.2-897.5)	486.4 (123.8-930.2)	0.0003
36	341.0 (109.6-680.8)	346.5 (155.7-517.1)	559.2 (262.0-795.1)	429.0 (51.7-885)	0.2130
48	325.4 (135.4-678.9)	311.0 (116.0-634.6)	503.3 (133.2-859.2)	439.1 (49.3-941.9)	0.3061
0.5-48	337.03 (74.9-860.3)	289.80 (31.2-724.5) [a, b]	578.88 (21.7-897.5) [b]	524.94 (5.4-1064.0) [a]	0.0002

*Numbers are means (range).
†P-values for comparing groups within interval.
[a,b]Groups with the same letter are significantly different after Tukey's procedure for multiple comparisons.

APPENDIX III: CPS

University of Melbourne Pain Scale

CATEGORY	DESCRIPTOR	SCORE
Physiologic Data		
a)	Physiologic data within reference range	0
b)	Dilated Pupils	2
c) Choose one	Percentage increase in heart rate	
	> 20%	1
	>50%	2
	>100%	3
d) Choose one	Percentage increase in respiratory rate	
	>20%	1
	>50%	2
	>100%	3
e)	Rectal temperature exceeds reference range	1
f)	Salivation	2
Response to Palpation		
Choose one	No change from preprocedural behavior	0
	Guards/reacts when touched	2
	Guards/reacts before touched	3
Activity		
Choose one	At rest – sleeping	0
	At rest – semiconscious	0
	At rest – awake	1
	Eating	0
	Restless (pacing, getting up and down)	2
	Rolling, thrashing	3
Mental Status		
Choose one	Submissive	0
	Overtly friendly	1
	Wary	2
	Aggressive	3
Posture		
a)	Guarding or protecting affected area	2

b) Choose one	Lateral recumbency	0
	Sternal recumbency	1
	Sitting or standing, head up	1
	Standing, head hanging down	2
	Moving	1
	Abnormal posture (hunched back, prayer position)	2
Vocalization		
Choose one	Not vocalizing	0
	Vocalizing when touched	2
	Intermittent vocalization	2
	Continuous vocalization	3