Effect of 4 Analgesic Protocols on Comfort and Sedation of Dogs for 24 hours after Stifle Surgery

THESIS

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By

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Abstract

Peri-operative and long-term pain management is essential for dogs undergoing TPLO. Combination analgesic techniques may be superior to individual techniques in dogs after stifle surgery. Pain and sedation scores were evaluated for 24 hours post-operatively in dogs undergoing TPLO surgery and assigned to 4 separate analgesia protocols. All dogs presented were chronically receiving an NSAID and NSAID administration continued post-operatively.

Thirty-four dogs presented for tibia plateau leveling osteotomy (same surgeon) were randomly assigned to one of four groups (four group repeated measure ANOVA): 1) Co-infusion of morphine (0.24 mg/kg/hr), lidocaine (3 mg/kg/hr), ketamine (0.6 mg/kg/hr) (MLK) begin at induction; 2) Lumbosacral epidural containing morphine (0.2 mg/kg) and ropivacaine (0.2 mg/kg) (LE) administered post-induction and pre-surgically; 3) MLK plus LE; 4) No additional analgesic drug administration after morphine premedication. All dogs received acepromazine (0.02 – 0.1 mg/kg) and morphine (0.4 mg/kg) intramuscularly (pre-medication), propofol, and isoflurane in oxygen (depth controlled by adjusting vaporizer setting). Indices of cardiorespiratory function and isoflurane requirement were recorded at 5-minute intervals during anesthesia which
included heart rate (HR), respiratory rate (RR), blood pressure, end-tidal carbon dioxide (ETCO₂), end-tidal isoflurane concentration (ETISO), and vaporizer percentage of isoflurane (ISO%). Co-infusion was discontinued at the end of surgery. A validated Sedation Scoring System and the Modified Glasgow Composite Measure Pain Score were used by two blinded evaluators to assess comfort and sedation after extubation and 98°F, at 60 minute intervals for 4 hours then every 4 hours for 24 hours. Dogs with pain scores greater than 6 were given morphine rescue analgesia (0.4 mg/kg, IM).

No differences in any intra-operative value; including, HR, RR, SAP, ETCO₂, ETISO, and Vaporizer % were detected among groups. No differences in pain score, rescue analgesia requirement, or time to first rescue analgesia were detected. Values (mean ± SD) for groups 1,2,3 and 4 were (respectively): Pain score: 2.6 ± 1.9, 2.6 ± 1.6, 2.8 ± 1.6, and 2.8 ± 2.0. Sedation score: 6.1 ± 4.3, 5.2 ± 4.3, 7.8 ± 4.5, and 6.3 ± 4.2 Rescue analgesia was administered to 4 of 12, 4 of 12, 5 of 12, and 3 of 12 dogs in each group for groups 1,2,3, and 4, respectively.

In conclusion, we found pain scores were similar among groups, and that all 4 groups had similar rescue analgesia requirements and had similar times to first rescue analgesia requirements. Because time to first rescue analgesia varied with each group we conclude that dogs undergoing TPLO surgery benefit from interval assessment of pain status throughout the 24 hour post-operative period.
Dedication

I dedicate this thesis to my brothers. Thank you for always being there and making me laugh.
“Life is pain, highness. Anyone who says differently is selling something.”

– The Princess Bride
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I would like to thank my entire faculty and all of the anesthesia section staff for their efforts and patience during this process. I would like to thank the OSU VMC classes of 2012 and 2013 for their assistance on anesthetizing the cases included in my study. I would like to especially thank Dr. Rich Bednarski. Without you, I wouldn’t be here today. Thank you again for all of time, advice and Kleenex. You’re the best.
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**Publications**


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Chapter 1: THE PAIN PATHWAY

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage (1). Nociception is defined as the neural processing and encoding of noxious stimuli. Nociception is an afferent activity produced in the nervous system as a result of endogenous or exogenous stimuli that cause tissue damage. The sensation of pain is a result of the response of neural receptors to damage or insult and the transmission of that response to the central nervous system (CNS) via anatomic pathways. The pain transmission pathway begins when a noxious stimulus activates nociceptors that transduce the inciting stimulus into an electrical signal (Fig 1.1) (1).
Figure 1.1: The Sensory Nervous System

Nociceptors are primary sensory neurons that detect and encode noxious stimuli and relay these signals to the CNS. They are free nerve endings with cell bodies in the
dorsal root ganglia and trigeminal ganglia outside of the spinal column. Nociceptors are located in tissues throughout the body including skin, muscle, periosteum, pleura, joint and bone. The nociceptor location determines the type of pain. For example, *Somatic pain* is caused by activation of nociceptors within the skin and musculoskeletal tissue while *visceral pain* is associated with activation of nociceptors within a body cavity. *Neuropathic pain* is related to nervous system damage. Nociceptors are activated by chemical, mechanical, or thermal stimuli. Chemical mediators that are released after tissue damage or inflammation can either activate or sensitize the nerve fibers. A-delta fibers are fast conducting (2-30 m/sec), thinly myelinated nerve fibers that detect sharp pain. These fibers are responsible for rapid reflex responses such as limb withdrawal from the inciting stimulus. C fibers slowly conduct (2 m/sec) nociceptive signals and are unmyelinated. Silent nociceptors are nociceptors that remain inactive until very high thresholds of inflammatory stimuli are breached, at which point they can be activated by many different stimuli at lower thresholds (1, 2). Potassium, serotonin, bradykinin, and histamine are activators of these afferent nerve fibers (1). Prostaglandins, leukotrienes, and substance P are sensitizers of these afferent nerve fibers (1).

Conceptually, nociception is divided into four steps. The first step is *transduction*, which involves the transformation of noxious thermal, chemical or mechanical stimuli into electrical signals (action potentials) that are propagated within peripheral A-delta and wide dynamic range C nerve fibers (*Fig 1.1*) (1). Cell and tissue damage releases
serotonin, bradykinin, norepinephrine, prostaglandins, adenyl triphosphate (ATP), histamine, hydrogen ions, substance P and nerve growth factor to act on specific receptors in the peripheral nerve terminals (2). Peripheral sensitization refers to a reduction in threshold and an amplification in the responsiveness of nociceptors. This occurs when the peripheral terminals of primary sensory neurons are chronically exposed to inflammatory mediators and damaged tissue. Sensitization is restricted to the site of tissue injury (1). Hyperalgesia is an exaggerated response to low intensity painful stimuli that is normally non-painful at the primary site of injury or in the secondary surrounding tissue that becomes inflamed (1). Increased responsiveness to non-noxious stimuli such as light touch, defined as touch-hyperalgesia (allodynia), can be a result of tissue damage (1). Hyperesthesia is an increased sensitivity to sensory stimulation (1).

The second step in the pain pathway is transmission which consists of conduction of the sensory impulses to the spinal cord (Fig. 1.1). Cell bodies of the first order A-delta and C nerve fibers are located in dorsal root ganglia. The axons of the cell bodies enter grey matter of the superficial spinal cord dorsal horn, ascend or descend for a few segments in the tract of Lissauer and terminate primarily in the superficial dorsal horn (marginal zone and substantia gelatinosa) (1, 2). Nociceptive afferent A-delta and C nerve fibers form direct or indirect connections with three classes of neurons: projection neurons which relay incoming sensory information to a higher center in the brain, excitatory interneurons, or inhibitory interneurons (1, 2).
Modulation, the third step in the pain pathway (Fig 1.1), occurs when interneurons within the spinal cord temper the relay of information to the projection neurons (2). Pain transmission is also altered by the descending inhibitory signals from the brain acting in the dorsal horn to modify nociceptive signals. The excitatory neurotransmitters in the dorsal horn are substance P, glutamate, prostanoids, serotonin, norepinephrine, acetylcholine, adenosine triphosphate (ATP), and brain derived neurofactor (BDNF) (1). The inhibitory neurotransmitters in the dorsal horn are gamma aminobutyric acid (GABA), opioids, alpha-2 agonists, adenosine, serotonin, norepinephrine, and kainite (1). Glutamate, the fast transmitter of primary afferent neurons, binds to several receptors on post-synaptic neurons in the dorsal horn of spinal cord, including amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), N-methyl-D-Aspartate (NMDA), and kainate (KA) receptors and several G-protein coupled glutamate receptor subtypes (mGluR) (1, 2). Substance P binds to the neurokinin-1 (NK1) G-protein–coupled receptor (1, 2). BDNF has a high-affinity for the trkB receptor (1, 2). Glutamate, Substance P and BDNF are mainly responsible for an increase in nerve excitability and responsiveness in the central nervous system, particularly in the spinal cord, called central sensitization or “wind-up” (1). Continued C-fiber dorsal horn stimulation increases the sensitivity of these neurons to nociceptive stimulation also resulting in allodynia and also chronic pain (2). Chronic pain persists longer than that
normally associated with healing of an acute condition or pain that is associated with a protracted condition (1).

*Perception* is the fourth and final step in the pain pathway. Perception involves impulses that have been projected to the brain and their processing and recognition (*Fig 1.1*) (1). Ascending nociceptive transmission results in the perception or awareness of pain localized to the anatomical location from which the stimulus arose. Perception evokes most of the autonomic and behavioral aspects of pain. Three different ascending pathways that mediate pain are the neospinothalamic tract, the paleospinothalamic tract and the archispinothalamic tract (3). Each pain tract originates in different spinal cord regions and ascends to terminate in different areas in the CNS (3).

The neospinothalamic tract is the classic lateral spinothalamic tract and contains few synapses. This tract’s input can either be from below the neck or above the neck. The first-order nociceptive dorsal root ganglion neurons from the body below the neck are located in the dorsal root ganglion synapse in the Rexed layer I neurons (3). Axons from layer I neurons ascend in the contralateral anterolateral tract to terminate in the ventroposterolateral nucleus (discriminatory) and ventroposteroinferior nucleus (somatosensory) of the thalamus (3). These portions of the thalamus serve as a relay station to send the signals to the primary cortex (3). The first-order nociceptive neurons from the head and neck have cell bodies located in the trigeminal ganglion (3). Trigeminal fibers enter the pons, descend to the medulla and make synaptic connections.
in the spinal trigeminal nucleus, cross the midline and ascend as trigeminothalamic tract. The A-delta fibers terminate in the ventroposteromedial thalamus, and the C fibers terminate in the parafasciculus and centromedian thalamus (3). This pathway is responsible for the immediate awareness and localization of a painful sensation (3).

The paleospinothalamic tract has first-order nociceptive neurons that synapse in Rexed layer II and the second-order neurons make synaptic connections in laminae IV-VIII (3). This tract is comprised of a wide dynamic range of nociceptors. The second-order neurons receive input from mechanoreceptors and thermoreceptors (3). The paleospinothalamic tract is comprised of three bilateral fiber tracts (3). Axons in this tract cross and ascend in the spinal cord as the anterior spinal thalamic tract which can synapse in: The mesencephalic reticular formation and in the periaqueductal gray (spinoreticular tract); The tectum (spinomedullary tract); Or in the parafasciculus and centromedian thalamus complex (spinothalamic tract) (3). The paleospinothalamic pathway also activates brain stem nuclei which are the origin of descending pain suppression pathways regulating noxious input at the spinal cord level (3). The multisynaptic tract has extensive connections between the limbic system and the cortex. This tract is involved in processing the emotional components of pain. The cortex integrates the sensory input with the cortical cognitive components to elicit response to the sensation, and the limbic structures initiate visceral responses to pain (3).
The archispinothalamic tract is a multisynaptic pathway (3). The first-order nociceptive neurons make synaptic connections in Rexed layer II and ascend within the spinal cord to laminae IV to VII (3). From here fibers ascend and descend in the spinal cord via the multisynaptic propriospinal pathway surrounding the grey matter to synapse with cells in the mesencephalic reticular formation and in the periaqueductal gray (3). This multisynaptic pathway ascends to the thalamus, the hypothalamus, and to the limbic system (3). This pathway mediates visceral, emotional and autonomic reactions to pain (3).

Pain is an adaptive mechanism to nociceptive input and neural stimulation. There are three components of the pain experience: sensory-discriminative, motivational-affective and cognitive-evaluative (1). Sensory-discriminative portions of the pain pathway reside anatomically in the lateral ascending nociceptive tracts of the spinal cord, thalamus, and somatosensory cortex. The sensory-discriminative pathway provides information on location, intensity, type, onset, and duration of the stimulus. Motivational-affective portions of the pathway reside in the medial ascending nociceptive spinal tracts and provide input into the limbic system. This input results in the unpleasant emotional experience associated with pain. The autonomic nervous system is closely linked with this portion. The reaction to the experience results in cardiovascular, respiratory and gastro-intestinal changes such as increases in heart and respiratory rates and decreased gastro-intestinal absorption (1, 2). The cognitive-evaluative portion of the pathway in the
cortical and reticular portions of the brain involves past experience or associations that have been made from prior encounters with a stimulus (1, 2).
Chapter 2: PAIN MANAGEMENT

Pain management eases suffering and improves the quality of life of those living with pain. It can prevent the detrimental autonomic responses that occur from pain such as increases in blood pressure and heart rate and decreases in immune functions (1). At each level of the pain pathway, distinct receptors are involved in the nociceptive process, which allows specific receptors to be targeted by analgesic drugs when managing pain (Fig 1.1). Understanding the receptors and neurotransmitters involved in the pain pathway is important for guiding the therapy selected for each patient and procedure. Pain control improves surgical outcomes if body systems are optimally functional instead of burdened by pain responses (1). Analgesia is a loss of sensitivity to pain. Analgesia can be initiated pre-operatively, intra-operatively and post-operatively.

Multimodal pain management is the term used for pain protocols that combine more than one analgesic drug type or technique in order to optimize pain control and minimize side effects associated with relatively large doses of a single drug. Multimodal analgesia has become the preferred method of pain control for invasive surgical procedures (1). Several review articles in both the human and veterinary literature, cite lower post-operative analgesia requirements, fewer side effects, faster healing times, and earlier hospital discharge times in patients receiving multimodal analgesia compared to
patients receiving only a single medication or one route of delivery (1, 4-8). The two categories of multimodal analgesia are multi-pathway analgesia and multi-pharmacologic analgesia. Different analgesic techniques are effective at different steps in the pain pathway, while different analgesics target different receptors within the pain pathway. Combinations of techniques and analgesics address the four steps in the pain pathway and blunt the detrimental pain responses while achieving optimal analgesia (Fig 1.1).

Most pre-operative anesthetic plans in veterinary medicine include a sedative or tranquilizer and an analgesic. Analgesic drugs administered pre-operatively can assist with restraint, provide preemptive pain control by targeting specific areas of the pain pathway, decrease induction drug requirements, and decrease intra-operative inhalant requirements. Pre-anesthetic analgesic drug administration can decrease the stress response elicited from surgery by reducing the amount of pro-inflammatory cytokines released resulting in a decreased intensity of the nociceptive response (9-11). Sedatives and tranquilizers administered pre-operatively help with restraint, produce muscle relaxation, decrease the amount of induction drugs required, and decrease peri-operative drug requirement. Some sedatives and tranquilizers may not provide analgesia, but may potentiate other analgesic drugs and their effects. The combination of sedatives or tranquilizers with an opioid (neuroleptanalgesia) produces a state of diminished awareness, decreased motor responsiveness, and decreased sensitivity to pain stimuli (1).
Although sedation can mask clinical signs of pain, sedation can also alleviate pain-associated anxiety (12).

Similar to analgesic premedication, intra-operatively administered analgesics can affect different steps in the pain pathway. Various routes of analgesic administration target different portions of the pain pathway. Some analgesics are given parenterally, epidurally, or as a constant rate infusion (CRI). The route of drug administration is largely determined by the surgical site and the properties of the drug itself. However, increasing the duration of action, reducing drug side effects, or titrating pain control are also reasons for a particular route of drug administration (13, 14, 15).

Intravenous analgesia will affect transduction, transmission and perception, while neuraxial administration of analgesic drugs can block or modify the pain transmission pathway and enhance descending modulation. Combining these two analgesic modalities may result in synergistic pain control (1, 16, 17, 18). Administration of analgesic and local anesthetic drugs into the epidural space and systemic analgesic drug infusions are effective forms of pain control that act specifically at the modulation and transmission portions in the pain pathway (1, 16, 17, 18, 19, 20, 21, 22, 23, 24). Epidurals and systemic infusions of analgesic drugs can be used safely together to control pain in surgical patients (25, 20, 16). Intravenous infusions of short-acting opioids can be administered to provide a consistent effective analgesic drug plasma concentration intra-operatively (14). The rate of infusion can be altered according to the patient response,
depth of anesthesia, and cardiopulmonary changes. Drug infusions can synergize with other analgesics to provide a more optimal level of pain control (10, 15). Infusions can reduce minimum alveolar concentration (MAC) of inhalation anesthetics and limit their cardiopulmonary depressive effects (25, 26).

Peri-operative local and regional anesthetic techniques focus analgesic delivery to the modulation, transmission, and transduction steps of the pain pathway. Systemic side effects are minimal because they are nerve or region specific and slowly absorbed. Examples of local infiltration are line blocks, ring blocks and splash blocks. Regional blocks are local nerve blocks associated with anatomic areas associated with a particular nerve targeted. Regional blocks include lumbosacral epidurals, brachial plexus blocks, and maxillary nerve blocks. Local and regional anesthetic techniques are very useful when a patient is a poor candidate for general anesthesia and can be useful adjuncts to any analgesic protocol.

Post-operatively administered analgesic drugs can prolong and enhance previously administered analgesic drugs. Pain due to swelling and inflammation from surgery can be treated with post-operative analgesic drugs (11). Again, the class of drugs being administered and route of administration can be tailored to the specific patient and type of surgery (ovariohysterectomy vs. orthopedic). Post-operative analgesia includes any analgesic drug formulation administered after surgery including orally administered
drugs, IV infusions, transdermal patches, and regularly and locally administered analgesics.
Chapter 3: MULTIMODAL ANALGESIC TECHNIQUES

The techniques of administration for multimodal analgesia include combinations of oral administration, parenteral injections and infusions, regional, local and neuraxial nerve blocks, and combining analgesics with sites of actions acting on different anatomical portions of the pain pathway.

3.1 Epidurals

Epidurally or intrathecally administered analgesic and local anesthetic drugs provide analgesia/anesthesia regionally depending on their volume and type of drug administered. Administration at the L7-S1 intervertebral space in dogs provides analgesia/anesthesia to the caudal portion of the body, generally caudal to the T13-L1 spinal segments. The anatomy of the epidural space in the lumbosacral region is described in the standard textbook of Anatomy (27) (Fig 3.1).
The meninges include the 3 fibrous membranes surrounding the spinal cord and brain. They are from outermost to innermost, the dura mater, the arachnoid, and the pia mater. The dura mater is tough and fibrous. The spinal dura mater consists of only one layer, the meningeal layer. The epidural space separates the periosteum of the vertebrae from the dura mater of the spinal cord. The arachnoid which lies immediately below the dura encloses the sub-arachnoid space that contains the cerebral spinal fluid. This space contains lymphatics, nerve roots, fatty tissue and the vertebral venous sinuses. The spinal cord terminates approximately 1 cm caudal to the fifth lumbar vertebrae in large breed dogs whereas small breed dogs’ spinal cords terminate at the lumbosacral vertebral

Figure 3.1: Canine Lumbosacral Epidural Diagram (27)
The subarachnoid space and dural sac extends approximately 2 cm beyond the end of the spinal cord.

In dogs, the epidural space is accessed most commonly at the lumbosacral intervertebral space which is an anatomic space between the 7th lumbar vertebrae and the 1st sacral vertebrae. A lumbosacral epidural is performed by inserting a needle through skin, subcutaneous tissues and ligaments overlying the vertebrae. There are three ligaments: the supraspinous, interspinous and intervertebral ligaments (ligamentum flavum), however, dogs have no supraspinous ligament and a poorly developed interspinous ligament at the level of the lumbosacral space (28). The thick connective tissue of the intervertebral ligament forms the dorsal aspect of the epidural space. Penetration of this ligament with the needle is associated with the “pop” or sudden loss of resistance noticed during needle placement. The lumbosacral epidural space is 2 to 4 mm in diameter in medium-sized dogs (28). The epidural space extends from the foramen magnum to the sacral hiatus. The length of the epidural space varies with the size of the animal (28).

Local anesthetics and opioids are most commonly used in epidurals. Many drugs including alpha 2 agonists, ketamine, benzodiazepines, NSAIDs and glucocorticoids have also been used epidurally (1). The inclusion of local anesthetics with an opioid in epidurals has a synergistic analgesic effect, providing more rapid onset and longer duration then when either is used alone (1, 29, 30, 31, 21, 32, 16, 18). Morphine epidurals
caused a MAC sparing effect in dogs anesthetized with halothane (33). Similarly, Troncy et al described the use of epidural morphine with and without bupivacaine in nearly 300 cases; they showed a significant MAC sparing effect in patients receiving morphine and bupivacaine combination epidurals compared to dogs receiving morphine only epidurals (29). Epidurally administered local anesthetics produce a 34-50% MAC sparing effect in people (34, 35).

Side effects of neuraxially administered drugs, including those administered epidurally, are largely dependent upon drug class, volume delivered, and cranial migration of the administered drugs (36, 37). The dose (in milligrams) is a function of the volume injected and the concentration of the solution, and the response is not necessarily the same if the same dosage is delivered in a different volume and concentration. The intensity of sensory blockade will increase as the volume of local anesthetic being delivered epidurally increases from 0.2 ml/kg to 0.6 ml/kg (38). The intensity of the sensory and motor blockade will increase as the concentration of the local anesthetic increases (21). Feldman et al demonstrated longer duration of motor blockade when the local anesthetic concentration increased from 0.5% to 0.75% (21). Duration of motor and sensory blockade demonstrated a dose-dependent relationship (21). The dose in humans required for analgesia or anesthesia is determined by several factors but generally, 1 – 2 mL of local anesthetic is needed per spinal segment to be blocked (37). A higher volume of a low concentration of local anesthetic will result in a larger number of segments
blocked but with less intense sensory and motor block. Whereas with a higher concentration of local anesthetic more sensory and motor blockade will occur (21, 37, 57). The spread of local anesthetic in the epidural space is unpredictable due to the variability in the size of the epidural space and the amount of local anesthetic that leaks into the paravertebral space. Sympathetic nerve fibers have the smallest diameter and are most easily blocked, even with low concentrations of local anesthetic, and the extent of sympathetic blockade is related to the number of spinal segments blocked.

Spinal anesthesia occurs when drugs are administered intrathecally. Without a reduction in local anesthetic dose that was calculated for lumbosacral epidural administration, intrathecal administration can result in depression or collapse of the cardio-respiratory systems. Local anesthetic spread to the cervical spinal cord and the first three thoracic spinal segments can result in hypoventilation, hypotension, and Horner's syndrome (1, 36, 37).

In general, the calculated total volume of drugs administered for a caudal epidural (caudal to T13-L1) is 0.2 mL/kg or 1 mL per 5 kg with a maximum of 6 mL (19, 20, 29). This dose will achieve sensory blockade up to the first lumbar vertebra. However, different drugs have been given at 0.13 to 0.36 mL/kg without adverse effects related to volume (28). Valverde has shown new methylene blue at a volume of 0.26 mL/kg delivered at the L-S space will spread to the 11th and 13th thoracic vertebrae in dogs (28). The risk of sympathetic and motor blockade increases with spread to the thoracic
spinal cord (1). When ten percent of the calculated volume is replaced with a 0.25% solution of ropivacaine, the dose fails to produce motor blockade yet provides sensory blockade (19, 20, 21, 29). The limit of 6 mL of total volume for large breed dogs is an assumption that the vertebral canal volume is not linearly related to body weight, but this has never been confirmed scientifically (28). The volume limit for epidurals may vary due to the concentration and combination of drugs being administered in the epidural space. A clinically safe epidural opioid dose is one tenth of the systemic dosage (29).

3.2 Co-infusions (MLK)

Analgesics can be administered as constant rate infusions and titrated according to patient response and overall analgesic plan. Drug combinations administered as co-infusions can provide multimodal analgesia due to multi-pathway and multi-pharmacologic action. Drugs that compete for the same receptor can have additive effects when each drug is used at a lower dose than that used during a single infusion (15). Co-administered drugs can exert a greater effect than when only one or the other drug is administered. Side effects of each of the drugs administered can be reduced with reduced dosages. Several drug combinations used in dogs can provide synergistic effects when administered intrathecally and intravenously (20). The intravenous co-infusion of morphine, lidocaine and ketamine shows both additive and synergistic effects when used to control pain (22). MLK causes a MAC sparing effect when administered to isoflurane
anesthetized dogs (25, 26). Morphine administered at a rate of 3.3 microg/kg/min was found to have the greatest MAC sparing effect of the 3 components in the MLK co-infusion (25).

To the author's knowledge, there has not been a comparison of analgesic effects in dogs associated with MLK infusion to that associated with epidural analgesia in dogs. Human literature fails to show additive or synergistic effects from combining fentanyl infusion with epidural analgesia compared to when each are applied separately (39). A study using methadone/ropivacaine epidurals showed improved post-operative analgesia in dogs undergoing TPLO surgery when compared to methadone alone epidurally (32). Clinically, it is unclear whether or not the combination of an infusion along with an epidural provides better analgesia than when either technique is applied separately.

3.3 Combination Parenteral Techniques (NSAIDs and opioids)

Dogs receiving a combined local anesthetic and opioid epidural plus an oral NSAID after cruciate surgery did not require rescue analgesia (31). This combination also provided better post-operative analgesia for 24 hours following administration, than the group without the oral NSAID (31). Dogs undergoing fracture repair who received an oral preoperative NSAID and a local anesthetic epidural had better post-operative analgesia than when only an oral NSAID was administered (40). Two other studies found dogs undergoing ovariohysterectomy and receiving an oral NSAID had significantly
lower pain scores and required less rescue analgesia than the opioid only group (41, 42).
These studies suggest that oral NSAIDs improve analgesia and decrease post-operative analgesia requirements when used in combination with other analgesics.
4.1 Inhalants

Inhalant anesthetics are delivered to and eliminated via the lungs. They can induce a state of general anesthesia and analgesia. The physical chemistry of a particular volatile anesthetic plays a role in the mechanism of action for each particular gas (15). A lot is unknown about the mechanisms and sites of action of inhalant anesthetics. Inhalant anesthetics disrupt normal synaptic transmission by interfering with the release of neurotransmitters from the pre-synaptic nerve terminal, alter re-uptake of neurotransmitters, change post-synaptic binding sites, and alter the flow of ions necessary for nerve conduction. They act on both pre-synaptic and post-synaptic sites and may have multiple concurrent sites of action. GABA\textsubscript{A} receptors may play a role in their mechanism of action. Inhalant anesthetics target the modulation and perception portions of the pain pathway \textit{(Fig 1.1)}. Sites of action in the brain affected by inhalant anesthesia include areas that control amnesia and hypnosis. The spinal cord is thought to be the site of anesthetic action associated with immobility due to modulation of excitatory and inhibitory neurotransmitters (1). Volatile gases provide analgesia via the spinal cord interaction. They inhibit the transmission of noxious stimuli to the brain. The degree of
analgesia provided is specific to each drug; methoxyflurane, isoflurane, and nitrous oxide rendering the best analgesia (15).

Minimum alveolar concentration (MAC) is the end-expired alveolar concentration of an anesthetic vapor at 1 Atmosphere that produces immobility in 50% of animals exposed to a supra-maximal noxious stimulus (1). This measurement is done after 15 minutes of alveolar concentration steady state, under the assumption that this amount of time allows for an equilibration between gases in the alveoli, the blood, and the brain (1). MAC is a measurement of inhalant anesthetic potency and is fairly constant among species and under varying conditions (1). The potency of a volatile agent is inversely proportional to its MAC. Various drugs and some extreme physical states may reduce or increase the inhalant requirement, causing a “MAC sparing” or “MAC increasing effect”. Drugs causing CNS depression decrease inhalant requirements and CNS stimulants increase inhalant requirements. Increased temperature and hypernatremia will increase inhalant requirements. Hypotension (BP <50 mmHg), temperature, hypoxemia (Pa02 < 40 mmHg), increasing age, pregnancy and high arterial carbon dioxide tensions will all decrease inhalant requirements. MAC does not change with duration of anesthesia or gender. Analgesic drugs can have MAC sparing effects in dogs (1).
4.2 Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs provide analgesia and suppress inflammation via the inhibition of the enzyme cyclooxygenase (COX), resulting in decreased prostaglandin synthesis. Specifically, they act on the transduction portion of the pain pathway to limit activation of peripheral nociceptors by reducing inflammation and within the brain to blunt the perception of pain (**Fig 1.1**). NSAIDs can provide analgesia comparable to that produced by opioids and they can also act synergistically with opioids allowing a reduction in opioid requirements in certain conditions and species (41, 42, 40). Yamashita *et al* demonstrated a MAC sparing effect with the use of NSAIDs and sevoflurane, and demonstrated that when these NSAIDs are used with an opioid they had additive MAC sparing effects (43).

NSAIDs are classified as COX selective, non-selective, or competitive. The non-selective NSAIDs have more adverse side effects than their selective counterparts. This is due to the diverse roles of COX enzymes. Cyclooxygenase is an enzyme that is responsible for the formation of prostanoids which in some instances maintain physiologic functions (constitutive) or perpetuate the inflammatory response (inducible). NSAIDs stop or diminish the production of prostanoids. The three main groups of prostanoids (prostaglandins, prostacyclins, and thromboxanes) are each involved in the inflammatory response. Prostanoids are a subclass of eicosanoids which are twenty carbons on a fatty acid signaling molecule. Prostaglandins are mediators of inflammatory
and anaphylactic reactions. Prostacyclins are active in the resolution phase of inflammation. Thromboxanes are mediators of vascular tone. At least two different COX enzymes exist; COX 1 and COX 2. COX 1 enzymes are constitutive, found in most cells and have day to day regulatory functions. COX 1 helps to maintain the normal lining of the gastrointestinal tract as well as kidney and platelet function. COX 2 enzymes are inducible, are produced in response to injury or fever and are involved in nociception. In the kidney, COX 2 is regulated in response to alterations in intravascular volume (2). COX 2 plays a role in the mediation of renin release, regulation of sodium excretion, and maintenance of renal blood flow (2). COX 2 is present at sites of inflammation. Both enzymes are involved in the arachidonic acid conversion to prostaglandin produced in response to pain and inflammation. It is less desirable to block COX 1 due to the numerous constitutive roles of COX 1. COX 2 selective NSAIDs have less side effects because they are less likely to disrupt normal activities. However, COX 2 inhibition may result in renal damage due to changes in renal blood flow (1, 2). Traditional NSAIDs, such as aspirin, are considered non selective because they inhibit both COX 1 and COX 2. The inhibition of COX 2 by traditional NSAIDs accounts for the anti-inflammatory effects of the drugs while the inhibition of COX 1 can lead to NSAID toxicity and associated side effects: ulcers, prolonged bleeding time, and kidney malfunctions. COX 2 selective NSAIDs were developed to reduce the side effects of traditional non-selective NSAIDs.
4.3 Opioids

Opioids are considered the gold standard in analgesia. Originally derived from the opium poppy (papaver somniferum), opioids are used to treat both acute and chronic pain. Opioids exert action at the transduction, modulation and perception portions of the pain pathway (Fig 1.1) (2). Opioid receptors are located in the brain (limbic system and periaqueductal grey matter), dorsal horn of the spinal cord, and periphery (1). Opioid analgesic effects can be titrated for the specific patient. They can be administered: parenterally, orally, and neuro-axially (44, 22). Long-term usage causes dependency and addiction in humans, but this has not been documented in animals (15). Opioid tolerance has been documented in several species after infusions of various opioids (15). Several studies have documented a MAC sparing effect in multiple species for many opioids (45, 46, 47). MAC sparing effects vary with type of opioid used, dosage, and route of administration; pure mu opioid agonists tend to have a greater MAC sparing effect than agonist-antagonists (46). Muir et al found morphine infusion peri-operatively reduced MAC by 48% and the combination MLK reduced MAC by 45% (25). This study also showed a reduction in MAC from lidocaine and ketamine individually, but not to the same degree as when an opioid was included in the infusion (25). Valverde et al showed epidural morphine reduced halothane MAC in dogs (33).

The normal physiologic pain response produces peptides that produce analgesic like effects in the central nervous system. These naturally occurring peptides mainly act
as neuromodulators and neurotransmitters and are present in different areas of the brain, pituitary, adrenal gland, gastro-intestinal tract and sympathetic nervous system (2). There are three families of these peptides; enkephalins, dynorphins and B-endorphin all of which have variable affinity to the receptor types (1). Opioids mimic the action of naturally occurring endorphins, enkephalins, and dynorphins synthesized by nerve cells; these substances decrease GABA neurotransmission. Opioids bind to opioid pre-synaptic and post-synaptic receptors located in the central and peripheral nervous systems and decrease perception of pain and increase pain tolerance (15). Most of their action is pre-synaptic causing decreased release of excitatory neurotransmitters (15).

The opioid receptors are G-protein coupled (Gs, Gi) and have inhibitory effects in the pain pathway. Opioid binding to the G-protein coupled receptor initiates a cascade of events leading to inhibition of synaptic transmission of nociceptive input, post-synaptic inhibition of ascending nociception and supra-spinal retrograde inhibition via descending anti-nociceptive pathways (1). All classes of opioid receptors are coupled to a G protein that inhibits adenyl cyclase and change fluxes in calcium and potassium. They diminish nociception acting on transduction, modulation, and perception (2). Endogenous opioids are also active in the descending pain modulation of neurons from the cortex, hypothalamus, periaqueductal grey area, and rostral medulla to alter pain response in the dorsal horn of the spinal cord (2).
Opioids exert clinical effects via activity at three different receptor types: mu, kappa, and delta. Mu activation is responsible for the opioid side effects such as bradycardia, hypoventilation, chemical dependency, GI side effects, and CNS depression (15). Agonists of the mu receptor are endorphins, morphine, and synthetic opioids. Kappa opioid receptors are associated with changes to calcium channel activity; dysphoria is linked to kappa activation (15). Kappa agonists are dynorphins and butorphanol. Delta agonists are enkephalins. There are various populations and distributions of opioid receptors throughout the body. Each opiate varies in affinity for receptor type as well as receptor location. Each opioid may also possess weak or strong binding affinity which is not correlated to effect of analgesia. For instance, buprenorphine has a high affinity to the mu receptor but exerts very little intrinsic activity (15).

There is a large population of mu and delta receptors in the mammalian brainstem that are responsible for opioid side effects. Opioids are respiratory depressants. In the medullary respiratory center of the brain, there is thought to be a respiratory rhythm generator which controls respiratory rhythm and pattern like a pacemaker (15). It has been proposed that opioids act via receptor-mediated ion channels at this respiratory pacemaker to reduce its control over respiratory muscles (15). They also exert effects on the vagal nuclei in the medulla which in turn causes bradycardia (15). Opioids may cause sedation prior to analgesia, cough suppression, nausea, vomiting, cutaneous vasodilation, altered thermoregulation, and gastrointestinal ileus in most species. Side effects will vary
depending on the chemical structure of the particular opioid, as well as the route by which the drug is administered, and the species. Full agonists tend to have more side effects than partial agonists.

4.4 Local Anesthetics

Local anesthetics block nerve conduction in all types of neurons, including all pain (A delta and C fibers), sensory, motor, proprioceptive, and sympathetic nerve fibers (1). Transduction, transmission and modulation portions of the pain pathway can be inhibited by local anesthetics (Fig 1.1). In addition, intravenous local anesthetics, particularly lidocaine, cause a MAC sparing effect (48). Valverde et al documented a MAC sparing effect in dogs with lidocaine infusions (49). In people a 34% MAC sparing effect occurs after local anesthetics are delivered epidurally (34). Muir et al showed a MAC sparing effect using an infusion of lidocaine (50 microg/kg/min) with or without a co-infusion with other analgesics (25). Ropivacaine differentially blocks nerve fibers in a dose dependent manner affecting less myelinated pain fibers (C and A-delta fibers) before more heavily myelinated sensory of motor fibers (1). Ropivacaine has a longer duration of action than lidocaine (1). Ropivacaine is used epidurally in low dose for sensory blockade (21).

The rate at which an impulse is transmitted along a nerve is dependent upon the diameter of its axon and the presence or absence of a myelin sheath. The minimum
concentration of local anesthetic necessary to block conduction is higher for more myelinated motor and proprioceptive nerve fibers than for less myelinated sensory nerve fibers. Additionally, local anesthetics must distribute for nodes of Ranvier along peripheral nerves to effectively cause blockade. Sensory anesthesia can occur without motor blockade. In mixed nerves generally mantle fibers are blocked before core fibers. The order of blockade is generally autonomic preganglionic B fibers, A-delta sensory fibers, C sensory fibers, A-beta sensory fibers, A-alpha motor fibers, and A-gamma proprioceptive fibers. The order of blockade varies with anatomical location, the specific nerve, or the local anesthetic used (1). Sensation is lost in in the following order: pain, cold, warmth, touch, joint, pressure. The potency, onset of nerve blockade, and duration of anesthesia are related to the degree of ionization of the local anesthetic molecule and lipid solubility.

There are two classes of local anesthetics; esters and amides. Metabolism varies depending on classification; but potency, duration of action and onset of action are a function of the individual local anesthetic drug. Local anesthetics act to block open voltage-gated sodium channels in nerve membranes reducing sodium ion influx and stopping propagation of action potentials (15). Disruption of nervous system conduction reduces or blocks autonomic, somatic sensory and somatic motor impulses leading to autonomic blockade, sensory anesthesia and paralysis of skeletal muscle (1). The active form of local anesthetics, the non-ionized base, diffuses across the axonal nerve
membrane where it blocks the generation and conduction of nerve impulses by inhibiting voltage-gated sodium channels. The degree of drug ionization depends on the local anesthetic's dissociation constant (pKa) and the surrounding tissue's pH. When the pKa and pH are identical, 50% of the drug is ionized and 50% is non-ionized. The dissociation constants of local anesthetics vary from 7.6 to 9.1, which means that less than 50% of local anesthetic exists in the active, non-ionized form at the normal tissue pH of 7.4 (1, 15). Local anesthetic duration of action will vary depending on chemical structure of the specific local anesthetic. Durations of action range from 30 minutes to 480 minutes (15). Duration of action of shorter acting local anesthetics, such as lidocaine, when deposited in tissue or neuraxially can be extended by adding drugs that cause vasoconstriction like epinephrine (1). Vasoconstriction keeps the local anesthetic in the tissues longer. The addition of opioids to local anesthetics in epidurals or spinals enhances and prolongs the duration of block (21, 50). Binding of local anesthetics to opioid receptors causes hyperpolarization of nerve membranes, which also decreases nerve impulse transmission. Animal experiments suggest that opioids and local anesthetic have a synergistic effect, but the mechanism is unknown (50).

Local anesthetics with faster absorption rates and shorter durations of action are associated with greater potential for systemic toxicity; bupivacaine is the exception to this statement. Bupivacaine has the greatest potential for cardiac toxicity. Side effects of local anesthetics involve the central nervous system, cardiovascular system, and local tissue.
effects. The systemic toxicity is correlated with the plasma concentration of the local anesthetic; CNS toxicities occur prior to cardiovascular toxicities (15). Side effects are typically the result of overdose, via large volume, high concentration or cranial migration of neuraxially administered local anesthetics.

Central nervous system (CNS) toxicity progresses through a continuum of excitation to coma. Initial signs are muscle twitching which can progress to convulsions and coma. CNS toxicity results from the depression of inhibitory cortical neurons in the brain which leaves excitatory pathways unopposed (1). The CNS toxicity may also be due to inhibition of neurotransmitter release, such as GABA (15).

Cardiovascular toxicity is related to a direct effect on electrical conduction or indirectly as a sequellae of CNS toxicity or maximal vasodilation and hypotension from neuraxially induced sympathetic block (1). This is generally seen as dysrhythmias, ventricular fibrillation, and cardiac arrest. CNS toxicity can result in increased heart rate and blood pressure during the excitement phase of toxicity, but direct cardiovascular toxicity results in a decreased heart rate and blood pressure (1). High plasma concentration levels will cause profound hypotension due to relaxation of arteriolar vascular smooth muscle and direct myocardial depression (15). Local anesthetic administration into the epidural or spinal spaces may result in depression of the cardioaccelerator nerves by spinally blocking thoracic segments, as the drug travels cranially (1).
Local anesthetics can cause damage to the nerve or other tissues in the area that the local anesthetic agent is administered. Both of these side effects are drug-specific, dose-dependent and correlated to frequency and duration of administration (1). Local anesthetics are more neurotoxic to sensory neurons by way of changing intracellular calcium concentrations (15). The toxicities to the nerve itself can be transient or persistent.

4.5 NMDA Receptor Antagonists

NMDA receptor antagonists such as ketamine inhibit the action of N-methyl d-aspartate receptors (NMDA). NMDA receptors are glutamate channels that control excitatory processes in the nervous system often activated with chronic pain (2). Ketamine is a noncompetitive NMDA receptor antagonist commonly used in human and veterinary medicine for dissociative anesthesia and analgesia. It binds to the phencyclidine receptor site when the channels are open (15). Nociception is modified via antagonism of the NMDA receptors present in the spinal cord and through cortical perception (Fig 1.1). Ketamine acts on several other receptor and electrolyte channels responsible for ascending and descending neurotransmission (15). It is available as a racemic mixture. The S-enantiomer has greater affinity for the NMDA receptor and is more potent than the R-enantiomer (15). Its NMDA receptor antagonism is responsible for its analgesic properties (15). Duration of action varies with species, route of
administration and dosage. Clinical effect lasts from 30 minutes to 2 hours when given intramuscularly or intravenously (15). There is a MAC sparing effect when ketamine is administered as an infusion in various species (25, 51), including dogs (52).

Ketamine affects the cardiovascular, respiratory, hepatic, and renal systems. It can increase intraocular and intracranial pressures. Antagonism of the NMDA receptor causes high concentrations of catecholamines, which indirectly stimulate the cardiovascular system (1). Increases in blood pressure, heart rate, and myocardial oxygen consumption are changes characterized during ketamine administration. An apneustic respiratory pattern frequently occur following ketamine administration. The ventilatory response to hypoxia is maintained (1). The duration of action of ketamine is prolonged in animals with hepatic and renal dysfunction (1). Muscle rigidity is associated with ketamine and is thought to cause transient increases in intraocular pressure (1). Ketamine is metabolized in the liver in dogs. An important active metabolite is norketamine. In dogs, norketamine is 1/5-1/3 as potent as ketamine and may prolong ketamine effects (15). Norketamine is excreted by the kidney. Hepatic and renal derangements may contribute to prolonged effects of norketamine and slowed clearance from the body (15).

4.6 Acepromazine

Acepromazine is a phenothiazine tranquilizer. It acts as an antagonist on post-synaptic dopaminergic receptors, serotonergic receptors, histaminergic receptors, alpha
receptors, and muscarinic receptors in the limbic system and basal ganglia collectively acting to relax and tranquilize (1). Acepromazine has a MAC sparing effect in various species including a 43% MAC sparing effect in dogs anesthetized with halothane (53, 54). Although not an analgesic drug, acepromazine does synergize with opioids and other analgesics to optimize analgesia (1). Acepromazine has a direct vascular effect and decreases mean arterial pressure, stroke volume, cardiac output and hematocrit (55, 56). Vasodilation is a result of alpha-1 adrenergic blockade (1). It causes little change in heart rate and respiratory function (56). It reduces incidence of emesis, is antihistaminic and antiarrhythmic, and increases glomerular filtration. (1). Barr et al showed decreased platelet aggregation after dogs were sedated with acepromazine (55). However, recent work by Conner et al found that acepromazine did not impact platelet function (57).
Chapter 5: PAIN ASSESSMENT

Pain assessment in non-verbal subjects is challenging (5, 6, 7, 22, 58 – 64). Pain is an individual and unique experience. Each individual may perceive and exhibit signs of pain differently. Personality, demeanor, environment and prior experience may contribute to this individual experience (65). Animals' responses to pain vary with species as well as with each individual’s disposition (1). For example, dogs will often vocalize while cats can become quiet and withdrawn. Since animals are unable to verbally express their comfort level, pain scoring systems have been devised that use objective and subjective components to assess pain (5, 6, 7, 22, 59 – 64). Physiologic factors such as heart rate, blood pressure, and respiratory rate generally increase in patients that are in pain. However, these physiologic parameters can also change due to non-pain factors such as anxiety, hypotension, hyperthermia, or hypothermia. Vocalization, restlessness, and body posture are subjective observations that can be used to judge pain in animals. The main impediment to developing an accurate pain scoring system in animals is their inability to speak. The gold standard in human pain scoring is the visual analogue scale because it is a self-reporting scale (66). Many studies have tried to validate a pain scoring system for use in animals (5, 6, 7, 22, 59 – 64).
There are a few validated pain scoring systems for veterinary patients. Validated pain scoring systems in veterinary patients are for very specific conditions and procedures and are species specific. They consist of simple descriptive scales, numerical rating scales, and visual analog scales. Simple descriptive pain scoring is the simplest form of assessment, using various descriptive categories and one of four to five descriptors per category (1). Numerical rating scales assign the descriptor a number. Numbers assigned to the various descriptors are totaled into a summative score. A visual analog scale is comprised of a 100 mm line where zero equals no pain and 100 equals the worst pain possible (1). The observer places a mark on the line and each subsequent reading is measured against the first mark. The University of Melbourne Pain Scale (UMPS), the Glasgow Composite Measures Pain Scale (GCMPS), the Modified Glasgow Composite Measures Pain Scale (MGCMPs), and 4A VET pain scoring system (4A VET) are the only reported validated veterinary pain scoring systems (1, 65, 67). They are all numerical rating scales (1, 65). The GCMPS is an orthopedic score in acute pain devised for dogs (58, 38), and is the only veterinary pain scale validated for hindlimb orthopedic acute pain scoring, although it has been modified to assess pain associated with other procedures without validation. A pilot study compared the Modified Glasgow pain scoring with the 4A VET pain scoring in dogs (67). The 4A VET pain scoring system relies on both physiologic and interactive components to assess pain. It takes into account a subjective assessment of overall pain, general attitude, interactive behaviors,
heart rate (percent increase from resting rate), and reaction and intensity to handling the
affected area (67). However, the physiologic variables used are not sensitive indicators of
pain severity (67). The 4A VET pain scoring was less biased by sedation but the
Modified Glasgow showed better inter-observer reliability (67). Validating means that
the chosen descriptors of pain reliably correlate to clinical signs of pain. The validated
pain scales in veterinary medicine are for acute pain only. A few studies have tried to
address scoring chronic pain but there are no scoring systems that address both acute and
chronic pain (66, 68). Up-regulation and neuroplasticity associated with chronic pain will
have an effect on pain responses.

Sedation can confound the results of pain scoring systems (54). Anxiety, however,
decreases pain perception thresholds. Balanced sedation and analgesia can be achieved
without overly sedating the patient and providing adequate anxiety relief. Sedation
scoring systems in the literature range from non-blinded, simple 1-to-5 scoring systems to
systems as detailed as the one used in the study reported here (69, 70). A more detailed
scoring system could not be located in the literature or independently derived. Sedation
was not found to affect GCMPS scoring (58). But it is reasonable to assume extreme
sedation would affect an animal's ability to overtly react to pain. A human study
demonstrated that sedation confounds pain scoring systems when used to evaluate
lumbosacral pain (71).
Chapter 6: TPLO SURGERY AND ANALGESIA

A tibial plateau leveling osteotomy (TPLO) is performed in dogs to neutralize cranial tibial thrust resulting from cranial cruciate ligament rupture (72, 73). During this procedure a crescentsic saw is used to perform an osteotomy of the proximal tibia. The proximal segment is rotated to change the tibial plateau angle; which stabilizes the stifle joint when the dog is weight-bearing. A bone plate and six to eight screws are implanted to stabilize the osteotomy. Recovery to functionality typically requires eight weeks (72).

Patients benefit from systemically administered opioid analgesia and epidural analgesia for controlling post-operative pain (29, 74, 72, 73, 16, 17). Although several analgesic protocols are used to treat post-operative orthopedic pain, no study has compared the multimodal analgesic protocols used in the present study (29, 74, 73, 16, 17). Literature review revealed that all 4 of the pain protocols in our study are commonly used in small animal veterinary practice. There is no gold standard for management of post-operative pain in TPLO patients. Most dogs presenting for TPLO surgery already chronically receive an NSAID that is continued post-operatively. Mu opioid receptor agonists are often used for the first 24 post-operative hours. A goal of this study was to find a clinically relevant perioperative analgesia protocol.
An examination of medical records at the OSU VMC revealed 285 TPLOs were performed from July 2010 through July 2011. Of these cases, 100% had received pre-operative opioids; 49% had an epidural and MLK infusion; 22.5% had an epidural alone; 15.8% had a MLK infusion alone, and 2% had no other analgesia other than a pre-anesthetic opioid. The remainder of the cases had incomplete data or variations on the analgesia protocols described. These records indicate that the pain protocols proposed by this study are commonly used in TPLO surgeries. The co-infusion of MLK was the most commonly used peri-operative infusion. These four protocols are widely used in TPLO surgery (71, 74, 75, 30, 76). As discussed previously, addressing nociception at several points in the pain pathway as well as at multiple receptors within the pathway should optimize pain management. Time points for data collection in the present study were chosen based on the 4 to 6 hour duration of analgesia provided by morphine.
Chapter 7 : SPECIFIC AIMS AND HYPOTHESIS

7.1 Specific Aims

The specific aims of this project were to determine if multimodal analgesia using MLK infusion plus lumbosacral epidural administration of morphine and ropivacaine is more effective in controlling orthopedic post-operative pain than either MLK infusion alone or epidural administration of morphine and ropivacaine alone. This study also determined the duration of post-operative analgesia from each of these protocols.

Based on current pain research, modifying the pain transmission pathway at several points is more effective in controlling pain than administration of a single analgesic protocol.

7.2 Hypothesis

The null hypothesis is no difference in pain scores in dogs receiving only morphine as a premedication, those receiving an epidural with morphine and ropivacaine, those receiving MLK, and those receiving MLK plus an epidural.
Chapter 8 : MATERIALS AND METHODS

8.1 Animals

The Ohio State University Clinical Research Advisory Committee approved this protocol. Client consent was obtained for each dog prior to surgery. Forty-eight adult client-owned dogs; weighing 34.8 to 44.5 kg, scheduled to undergo a tibial plateau leveling osteotomy of the stifle joint for a cranial cruciate ligament rupture were enrolled in the study. Dogs were healthy, based on physical examination, hematologic evaluation, serum biochemical analysis, and urinalysis. Concomitant medication administration (e.g. NSAIDs, nutraceuticals, heartworm preventative, or hormone replacement therapy) was recorded. If the patient had been sedated the day prior to surgery for radiographs, the type and dosages of drugs were recorded.

8.2 Anesthesia and Surgical Procedure

A physical examination was performed on each dog the day of the surgery. Temperature, pulse, respiratory rate, weight, mucous membrane color, hydration status, and American Society of Anesthesiologists preoperative status were determined and recorded on the anesthetic record. Any other additional medications the patient was currently receiving were also recorded.
Food, but not water, was withheld for 12 hours prior to anesthesia. Dogs were premedicated intramuscularly with 0.02 - 0.1 mg/kg (3 mg maximum dose) acepromazine and 0.4 mg/kg morphine 20 minutes prior to IV catheterization and induction. A dose range was allowed for acepromazine so that sedation could be tailored to each patient. An 18 or 20 gauge catheter was inserted into a cephalic vein for drug and fluid administration. Dogs were induced with intravenous propofol (4 mg/kg), given to effect and a total dose was recorded. Dogs were oro-tracheally intubated and maintained using isoflurane. Oxygen was used as the carrier gas using an out of circuit precision vaporizer and a semi-closed circle system. Initial vaporizer settings were adjusted by the anesthetist according to clinical interpretation of anesthetic depth. Typically isoflurane 3% and oxygen 1-3 L/min were used for the first 3-5 minutes. Subsequently isoflurane vaporizer settings were adjusted to 1% - 2% with an oxygen flow rate between 10 and 40 mL/kg/min. Intravenous lactated Ringers solution was administered at 5 mL/kg/hour from the time of catheter insertion throughout the surgical procedure and discontinued when the skin was being sutured.

Dogs were mechanically ventilated at 6 to 8 breaths per minute and 10-15 mL/kg tidal volume to maintain end-tidal partial pressure of CO₂ between 35 and 45 mm Hg. Mechanical ventilation was initiated when the dogs were transferred to the surgical suite and was discontinued prior to transfer to radiology for post-operative radiographs.
Cardiovascular support, when needed, consisted of IV administration of glycopyrrolate (5-10 ug/kg) or dopamine (1-5 ug/kg/min) for treatment of bradycardia or hypotension, respectively. Bradycardia was defined as a heart rate less than 55 beats per minute and hypotension as systolic arterial blood pressure less than 80 mmHg for longer than 5 consecutive minutes.

If dysphoria occurred during recovery, acepromazine (0.02 - 0.05 mg/kg) was administered IV. Morphine (0.4 mg/kg IM) was administered to all patients whose post-operative pain score was greater than 5 out of 24. Patients were allowed to have NSAIDs at any time during the study; the type of NSAID, dosage, and time(s) administered were recorded.

The same surgeon (JD) performed all surgeries. An arthrotomy was performed, and tibial plateau leveling osteotomy was used to stabilize the stifle joint.

8.3 Experimental Design

A blinded, randomized parallel design was conducted. Dogs were randomly assigned to 1 of 4 analgesia protocols: Group-1 MLK infusion (morphine (0.24 mg/kg/hr), lidocaine (3 mg/kg hr), and ketamine (0.6 mg/kg /hr)). Group-2 epidural [(morphine (0.2 mg/kg) + 1 % ropivacaine (0.2 mg/kg)]; Total volume delivered was 1 mL/4.5 kg body weight to a maximum of 10 mL.) Group-3 MLK infusion and an
epidural (morphine + 1 % ropivacaine). Group-4 no additional analgesia other than the morphine premedication.

A loss of resistance technique and palpation of appropriate landmarks was used to guide epidural needle placement at the L7-S1 intervertebral space (25) (Fig 3.1). One of four anesthesiologists or one of four anesthesia technicians performed all of the epidurals. All dogs were clipped over the normal epidural site and the site was covered with a bandage in the post-operative period to prevent bias during pain scoring.

The two individuals collecting data were not allowed contact with the patient until Time 0 and also had no access to anesthetic records.

8.4 Physiologic Monitoring

Shortly after induction, a doppler probe was placed over a palmer digital artery for pulse rate detection and an estimation of systolic arterial blood pressure (SBP) using an appropriate sized cuff proximal to the doppler. Heart rate (HR), respiratory rate (RR), and systolic pressure by doppler were recorded. While in the surgery room, an oscillometric blood pressure monitor and appropriately sized cuff were attached to a peripheral limb for measurement of systolic (SBP), diastolic (DAP), and mean arterial pressure (MAP). End tidal CO₂ (ETCO₂) and end tidal isoflurane (ETIs) were obtained from a multi-gas analyzer display. A lead II ECG was used to monitor heart rhythm. Body temperature was measured using an oropharyngeal thermistor probe. Body
temperature was maintained with the use of a circulating warm air blanket positioned under the surgical drapes and over the thorax of each dog. Data were obtained and recorded every 5 minutes from anesthetic induction through termination of surgery. The duration of total anesthesia, total surgical time, and time of endotracheal tube removal were recorded. Time to extubation is defined as the time from the vaporizer being turned off until the endotracheal tube was removed.

If a dog exhibited signs of response to surgical stimulation (marked and sudden increase in HR, MAP, or both or movement) intra-operatively and could not be maintained by increasing isoflurane concentrations, rescue analgesia (hydromorphone 0.02mg/kg IV) was given. These dogs were removed from the study.

8.5 Pain and Sedation Assessment

Assessments were performed by 1 of 2 trained evaluators (KL, VN). Assessments began after surgery and removal of the endotracheal tube when the patient was at least 98.1°F (Time 0). Pain and sedation scores were recorded at Time 0, at 60 minute intervals for the first 4 hours, and then every 4 hours for the 24 hours post-operative time. A Modified Glasgow Pain Scoring Method (MGPSM) was used to assess pain scores in all of the patients. (Appendix A) Variables assessed included vocalization, attention to wound area, mobility, response to touch, demeanor and posture. If any patient received a pain score of 6 or higher, rescue analgesia with morphine (0.4 mg/kg IM) was
administered. The frequency of administration and total dose of rescue analgesia was recorded.

A validated sedation scoring system (SSS) was used to assess sedation in all of the patients (Appendix B). Variables assessed included vocalization, posture, appearance, interactive behaviors, restrain-ability, and noise response. Sedation and pain were evaluated at each time point. The sedation score results were recorded but did not affect whether the patient received analgesia.

8.6 Data Analysis

Data was tested for normality graphically (by visual inspection of histograms and residual plots) and formally (using the Shapiro-Wilks test). If the data were not normally distributed the data were transformed to normalcy or a non-parametric analysis (e.g. Kruskal-Wallace test) was applied. Differences between pain scores were tested by using a nested-factorial analysis of variance (ANOVA) if successfully transformed to normalcy. Design: 4 treatment groups = fixed variable; 12 patients = random variable nested within each group; 10 times = fixed variable (crossed with group and applied to each patient). Two-sided tests were used to allow the possibility of detecting unexpected relationships and the alpha was set at 0.05. All significant differences between more than 2 groups (or patients or times) were followed up with appropriate multiple comparison
procedures (e.g. Newman-Keuls procedure if the data were normally distributed) to
determine exactly which protocols were different.
Chapter 9: RESULTS

9.1 Animals

Seventeen breeds were represented in this study, including 14 mixed-breed dogs, 6 Labrador Retrievers, 5 Golden Retrievers, 4 German Shepherds, 3 Great Pyrenees, 3 Newfoundlands, 2 American Bulldogs, 2 Rottweilers and 1 dog each for 9 other breeds (Table 9.1). Treatment groups did not differ significantly with regard to ASA status, body weight, sex distribution, or age (Table 9.2).

Table 9.1: Breeds

<table>
<thead>
<tr>
<th>MLK</th>
<th>LE</th>
<th>MLK + LE</th>
<th>M only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bearded Collie</td>
<td>American Bulldog – 2</td>
<td>German Shepherd – 2</td>
<td>Dalmatian</td>
</tr>
<tr>
<td>Chow</td>
<td>American Cocker Spaniel</td>
<td>Golden Retriever – 3</td>
<td>Great Pyrenees</td>
</tr>
<tr>
<td>German Shepherd</td>
<td>Catahoula Leopard Hound</td>
<td>Labrador Retriever</td>
<td>Labrador Retriever – 3</td>
</tr>
<tr>
<td>German Shorthair Pointer</td>
<td>Doberman Pinscher</td>
<td>Mixed Breed – 5</td>
<td>Mixed Breed – 4</td>
</tr>
<tr>
<td>Golden Retriever</td>
<td>German Shepherd</td>
<td>Newfoundland</td>
<td>Rottweiler – 2</td>
</tr>
<tr>
<td>Great Dane</td>
<td>Golden Retriever</td>
<td></td>
<td>Siberian Husky</td>
</tr>
<tr>
<td>Great Pyrenees – 2</td>
<td>Labrador Retriever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labrador Retriever</td>
<td>Mixed Breed – 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed Breed – 2</td>
<td>Newfoundland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newfoundland</td>
<td></td>
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</table>
Table 9.2: Demographics (Mean ± SD for weight and age)

<table>
<thead>
<tr>
<th></th>
<th>MLK</th>
<th>LE</th>
<th>MLK + LE</th>
<th>M only</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA status</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>44.5 +/- 18.0</td>
<td>34.8 +/- 12.1</td>
<td>40.0 +/- 12.4</td>
<td>35.0 +/- 10.6</td>
</tr>
<tr>
<td>Gender FS/MC</td>
<td>7/5</td>
<td>4/8</td>
<td>6/6</td>
<td>6/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>5.0 +/- 1.9</td>
<td>7.2 +/- 2.4</td>
<td>6.7 +/- 3.0</td>
<td>5.3 +/- 3.2</td>
</tr>
</tbody>
</table>

9.2 Perioperative NSAIDs, Acepromazine dosages, and Intraoperative Values

Five different NSAIDs were represented in this study. The distribution of NSAID use was not different among groups (Table 9.3). Carprofen was the most common NSAID used. The dose of acepromazine used to for sedation was not different among groups (Table 9.4). Mean +/- SD dose of acepromazine was between 0.05 - 0.06 +/- 0.02 mg*kg-1 for all groups. The dose of propofol was 4 mg*kg-1 for all groups. The mean +/- SD of the intra-operative values, including HR, RR, SBP, ETCO₂, ET₁₀, vaporizer percentage at induction, and vaporizer percentage during the surgical period were not
different among groups (*Figures 9.1, 9.2, 9.3, 9.4, 9.5, 9.6*). The median +/- interquartile data of the HR, RR, SBP, and vaporizer percentages are shown for each group during the induction and surgical periods (*Fig 9.7*).

**Table 9.3: Peri-operative NSAIDs**

<table>
<thead>
<tr>
<th></th>
<th>MLK</th>
<th>LE</th>
<th>MLK + LE</th>
<th>M only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carprofen</td>
<td>7</td>
<td>9</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Deracoxib</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Firocoxib</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>1: Meloxicam</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1: Piroxicam</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 9.4: Mean acepromazine dosages (mg*kg -1)**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MLK</td>
<td>0.06 +/- 0.02</td>
</tr>
<tr>
<td>LE</td>
<td>0.05 +/- 0.02</td>
</tr>
<tr>
<td>MLK + LE</td>
<td>0.05 +/- 0.02</td>
</tr>
<tr>
<td>M only</td>
<td>0.06 +/- 0.02</td>
</tr>
</tbody>
</table>
Figure 9.1: Mean heart rate (HR)
Figure 9.2 Mean respiratory rate (RR)
Figure 9.3 Mean systolic blood pressure (SBP)
Figure 9.4: Mean end-tidal carbon dioxide
Figure 9.5: Mean vaporizer percentage isoflurane (ISO%)
Figure 9.6: Mean end-tidal isoflurane concentration
Figure 9.7: Median HR, RR, SBP, ISO % by group
9.3 Duration of anesthesia, surgery, time to extubation, and rescue analgesia

Duration of anesthesia, duration of surgery and time to extubation were not different among groups (*Table 9.5*). *Figure 9.7* illustrates the median +/- interquartiles of the surgery time among groups. Dogs in each group received rescue analgesia over the 24 hour post-operative period (*Fig 9.8*). A Kaplan Meier time to rescue curve denotes the percentage of dogs without any rescue analgesia remaining over time in each treatment group (*Fig 9.8*). Numbers of dogs requiring rescue analgesia, time to rescue analgesia administration, average dose of rescue analgesia, or average number of rescue analgesia doses were not different among groups (*Table 9.6*). *Tables 9.7 – 9.10* provide information on dogs that received rescue analgesia in each group and at which pain scoring time points they received rescue analgesia. Five dogs were removed from the study prior to pain scoring. One dog was removed due to a skin infection over the surgical site. Three dogs were removed during surgery due to complications in the surgical procedure itself, which did not impact the anesthetic episode. Lastly, one dog was removed during the post-operative period because additional drugs were inadvertently administered. Data analysis was performed on the 48 dogs enrolled in the study.
### Table 9.5: Mean Duration of anesthesia, duration of surgery, time to extubation

<table>
<thead>
<tr>
<th></th>
<th>MLK</th>
<th>LE</th>
<th>MLK + LE</th>
<th>M only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Anesthesia</td>
<td>145 +/- 28</td>
<td>137 +/- 20</td>
<td>142 +/- 20</td>
<td>135 +/- 18</td>
</tr>
<tr>
<td>(minutes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Surgery</td>
<td>72 +/- 25</td>
<td>61 +/- 18</td>
<td>59 +/- 9</td>
<td>58 +/- 7</td>
</tr>
<tr>
<td>(minutes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to Extubation</td>
<td>21 +/- 15</td>
<td>16 +/- 16</td>
<td>43 +/- 31</td>
<td>18 +/- 12</td>
</tr>
<tr>
<td>(minutes)</td>
<td></td>
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</tr>
</tbody>
</table>
Figure 9.8: Median surgery time (minutes) by group
Figure 9.9: Kaplan Meier time to rescue curve
### Table 9.6: Rescue Analgesia

<table>
<thead>
<tr>
<th></th>
<th>MLK</th>
<th>LE</th>
<th>MLK + LE</th>
<th>M only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number rescued</td>
<td>4/12</td>
<td>4/12</td>
<td>5/12</td>
<td>3/12</td>
</tr>
<tr>
<td>Average time to analgesia</td>
<td>5.6 hours post-op</td>
<td>7 hours post-op</td>
<td>4.6 hours post-op</td>
<td>13.7 hours post-op</td>
</tr>
<tr>
<td>administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average dose of rescue</td>
<td>26.25 mg (0.4 mg/kg)</td>
<td>18.75 mg (0.4 mg/kg)</td>
<td>16.56 mg (0.4 mg/kg)</td>
<td>31.5 mg (0.4 mg/kg)</td>
</tr>
<tr>
<td>analgesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average number of rescue</td>
<td>2.8</td>
<td>2.3</td>
<td>1.6</td>
<td>3</td>
</tr>
<tr>
<td>analgesia doses</td>
<td></td>
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### Table 9.7: MLK group rescue analgesia requirements

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<th>2</th>
<th>3</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
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<tbody>
<tr>
<td>Molly</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Gracie</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<td>Dozer</td>
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### Table 9.8: LE group rescue analgesia requirements

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<th>3</th>
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<th>12</th>
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<tbody>
<tr>
<td>Greta</td>
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<td>X</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Miley</td>
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<td>X</td>
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<tr>
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### Table 9.9: MLK + LE group rescue analgesia requirements

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<tr>
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<td></td>
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<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Stella</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Rylee</td>
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<td></td>
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<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Harley</td>
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<td>X</td>
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### Table 9.10: M only group rescue analgesia requirements

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<tbody>
<tr>
<td>Dakota</td>
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<td></td>
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<td></td>
<td></td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<td>Ben</td>
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<td></td>
<td></td>
<td></td>
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<td>X</td>
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</tr>
</tbody>
</table>
9.4 Sedation and Pain Scores

The maximum sedation score possible was 14. Mean sedation scores ranged from 5.2 – 7.8. Sedation scores among groups were not different (Table 9.11). Sedation decreased over time and at the same rate among groups (Fig 9.9). Figure 9.10 illustrates the group and sedation scores over time. The maximum pain score possible was 24. When pain scores were averaged over time, they ranged from 2.6 – 2.8 with no difference among groups for mean pain score (Table 9.12). Median and mean pain scores among groups were not different over time (Fig 9.11, Fig 9.12, Fig 9.13). Pain scores were plotted against a maximum score; no group had a mean pain score that was greater than 7 (Fig 9.14).

Table 9.11: Mean sedation scores among groups. Maximum score 14.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Sedation Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLK</td>
<td>6.1 +/- 4.3</td>
</tr>
<tr>
<td>LE</td>
<td>5.2 +/- 4.3</td>
</tr>
<tr>
<td>MLK + LE</td>
<td>7.8 +/- 4.5</td>
</tr>
<tr>
<td>M only</td>
<td>6.3 +/- 4.2</td>
</tr>
</tbody>
</table>
Figure 9.10: Mean sedation scores over the 24 hour post-operative period.
Figure 9.11: Median sedation score over time by group.
Table 9.12: Mean pain score. Maximum score 24.

<table>
<thead>
<tr>
<th></th>
<th>Pain Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>[ALL DOGS]</strong></td>
<td></td>
</tr>
<tr>
<td>MLK</td>
<td>2.6 +/- 1.9</td>
</tr>
<tr>
<td>LE</td>
<td>2.6 +/- 1.6</td>
</tr>
<tr>
<td>MLK + LE</td>
<td>2.8 +/- 1.6</td>
</tr>
<tr>
<td>M only</td>
<td>2.8 +/- 2.0</td>
</tr>
<tr>
<td><strong>[WITHOUT RESCUED DOGS]</strong></td>
<td></td>
</tr>
<tr>
<td>MLK</td>
<td>2.0 +/- 0.9</td>
</tr>
<tr>
<td>LE</td>
<td>2.2 +/- 1.0</td>
</tr>
<tr>
<td>MLK + LE</td>
<td>2.0 +/- 1.1</td>
</tr>
<tr>
<td>M only</td>
<td>2.1 +/- 1.0</td>
</tr>
</tbody>
</table>
Figure 9.12: Median pain score by group
Figure 9.13: Mean pain score
Figure 9.14: Mean and median pain scores among groups over time
Figure 9.15: Mean pain score out of maximum score 24.
Chapter 10 : DISCUSSION

The response to pain created by TPLO surgery was similar among the 4 groups and the results of our study indicate that: 1) No differences were found among groups for mean pain score and mean pain scores among groups were not different over time; 2) No differences were found among groups in the number of dogs requiring rescue analgesia, the time to first rescue analgesia administration, the average dose of rescue analgesia, or the average number of rescue analgesia doses among groups; 3) There were no differences in sedation scores among groups; and 4) The intra-operative values, including HR, RR, SBP, ETCO₂, ET₆₀, vaporizer percentage at induction and vaporizer percentage during the surgical period were not different among groups.

Our pain score results are contrary to those from other studies comparing analgesia protocols in orthopedic procedures in the 24 hour post-operative period (16, 18, 77). Hendrix et al compared 4 analgesic groups: 0.5 % bupivacaine epidural, morphine epidural, morphine plus bupivacaine epidural, and saline epidural. All groups received an opioid as a premedication and the epidural was administered post-operatively. This study found that pain scores were lower in dogs receiving the combination epidural, that the time to administration of rescue analgesia was longer for dogs in the combination epidural group and that the number of rescue analgesia boluses administered was lower in
the combination groups than in dogs receiving a saline epidural (18). The higher concentrations of local anesthetic used in their combination epidurals may have provided better analgesia therefore showing a difference in pain scores among groups. The concentration of local anesthetic used in their study provided motor blockade. Complete sensory blockade will be achieved before motor blockade occurs (15). Hendrix et al allowed any combination of sedative and opioid as a premedication but our premedication protocol was standardized. Various durations of action of opioids could have accounted for the time to rescue analgesia results in Hendrix’ study. Lastly, the surgical procedures were not standardized in the Hendrix study; any orthopedic procedures involving the hindlimbs or pelvis were included in their study. Less traumatic orthopedic surgical procedures, such as lateral suture placement, would require less post-operative analgesia than for example a multi-trauma pelvic fracture. These differences in study design may account for their results showing combination epidurals provide better post-operative analgesia while our study did not.

The study by Kona-Boun et al used either oxymorphone (0.1 mg/kg) or hydromorphone (0.2 mg/kg) with acepromazine (0.05 mg/kg) intramuscularly as a premedication. The groups that were investigated were morphine and 0.5% bupivacaine combination epidural, morphine only epidural, and saline only epidural. This study found the morphine and bupivacaine combination epidural group had lower values for intraoperative arterial blood pressure, isoflurane requirements, post-operative pain scores,
rescue analgesia requirements, and plasma cortisol concentrations (16). The concentration of local anesthetic used in their combination epidurals may be the reason we did not find a differences in pain scores in our study. Kona-Bon et al also did not standardize the orthopedic surgical procedure which could impact post-operative analgesia requirements.

Bosmans et al recently published a study in dogs undergoing tibial tuberosity transposition, comparing post-operative analgesia with a methadone and ropivacaine combination epidural to a methadone only epidural, with or without oral NSAID administration (77). They used a standardized premedication of acepromazine (0.01 mg/kg) and methadone (0.1 mg/kg) intravenously. In this study, dogs that received an orally administered NSAID plus combination methadone and 0.75% ropivacaine epidural required less intra-operative rescue analgesia, had lower isoflurane requirements, and an extended analgesia duration compared to the methadone only epidural group (77). Methadone works at opioid and NMDA receptors in the pain pathway. Bosman et al also used a higher concentration of local anesthetic in their combination epidurals. These two differences in drugs may be reasons for our study results.

Hoelzler et al compared the combination of morphine and 0.5% bupivacaine epidural plus hydromorphone (0.05 mg/kg IV), 0.5% bupivacaine intra-articular splash block plus hydromorphone (0.05 mg/kg IV) and hydromorphone (0.05 mg/kg IV) alone in dogs undergoing TPLO surgery; they found duration of analgesia was longer in dogs
receiving an epidural or intra-articular analgesia (74). Dogs receiving an epidural required fewer doses of rescue analgesia than dogs receiving intravenous analgesia. A higher concentration of local anesthetic was used which could result in differences in pain scores found in their study.

From these studies we surmised that the groups receiving an epidural in our study would have lower intra-operative isoflurane requirements, longer analgesia durations, and less rescue analgesia requirements than groups without epidurals. Due to the duration of action of the drugs in MLK infusion, we also hypothesized that the MLK infusion would provide longer durations of analgesia than the group which only received morphine as a premedication. The lack of MAC study design, the standardized premedication protocol, the time of epidural administration (pre-operative vs. post-operative), the concentration of local anesthetic in the epidural (motor blockade concentration vs. sensory blockade concentration), and the short duration of surgery may explain why, in contrast to those studies, we found no differences in intra-operative variables, pain scores, and rescue analgesia frequency and duration.

Labrador retrievers or Labrador crossbreds, Rottweilers and Rottweiler crossbreds, German shepherds and shepherd crossbreds, along with Golden retrievers are breeds prone to cranial cruciate ligament rupture (78, 79). Of the seventeen breeds of dog represented in our study, 17 of the 48 dogs enrolled in this study were Labradors, Rottweilers, German Shepherds and Golden retrievers (Table 9.1) and these breeds were
evenly represented among the 4 groups. These breeds are generally considered relatively stoic and manageable compared to some other breeds. Body weight, age, gender distribution, and ASA status were not different among groups (Table 9.2). All dogs were either an ASA status of 1 or 2. Gender distribution included only castrated male and spayed female dogs in each group. The average age ranged from 5 years to 7.2 years among groups. The average weight ranged from 34.8 kg to 44.5 kg among groups. These age and weight distributions are in agreement with ages and weights typical of dogs requiring TPLO surgery (79). There was no difference among groups in gender distribution or age. The stoic demeanor of this overrepresented population of dogs may have impacted analgesia requirements and pain scores in the present study. As in most studies that examine pain in animals, it is possible that some dogs were more painful than judged to be, and that others suffered from behaviors such as separation anxiety and were judged as more painful than they really were. Demeanor and personality can affect pain response and an overrepresented breed type or gender could skew pain scoring data or contribute to minimal differences among groups (80, 81). The criteria to assess pain were applied equally to all dogs and this may explain the large standard deviations seen in our data. It could be proposed that because our population consisted largely of stoic breeds, this might have resulted in the observed uniformly low pain scores.

Sedation can affect pain scoring even though the MGCMPs was shown to be less affected by sedation than other scoring systems (54, 58, 66, 82). There was no significant
difference among groups in the acepromazine dosage used to tranquilize the dogs within each group (*Table 9.4*). Dosages (mg/kg) ranged from 0.06 ± 0.02, 0.05 ± 0.02, 0.05 ± 0.02, and 0.06 ± 0.02 for the MLK group, the LE group, the MLK + LE group and the M only groups respectively. Although there is individual variance with impact of drug, there was no difference in acepromazine dosages among groups. Therefore all groups were comparably sedate and it had no influence on our comparative results. Pre-operative temperaments in each group were similar, further supporting no pre-operative temperament differences among groups. Other studies comparing analgesia protocols in dogs undergoing orthopedic surgery, did not address the influence of acepromazine premedication dosages (0.05 mg/kg) on their pain protocols (31, 40, 41, 42, 74). The duration of action of acepromazine is 4 to 6 hours (1).

All dogs in the present study chronically received an NSAID chronically prior to presentation, and all dogs were administered an NSAID at extubation. The NSAID-associated anti-inflammatory and analgesia properties could have contributed to masking differences in analgesia among groups in our study. It is possible we underestimate the analgesic effects of NSAIDs for orthopedic procedures. Carprofen (Rimadyl) was the most commonly administered NSAID (*Table 9.3*). The MLK group, the LE group, the MLK + LE group and M only group had 7, 9, 7, and 5 of the 12 dogs respectively receiving carprofen. Several studies have shown the analgesic efficacy of NSAIDs used in conjunction with opioids (31, 40, 41, 42, 43, 83, 84, 85, 86). Carprofen administered
alone to dogs undergoing ovariohysterectomy produced similar analgesia and pain scores over a 24-hour period compared to dogs that received both carprofen and morphine (87). Fowler et al showed that the addition of meloxicam parenterally to epidural morphine improved pain scores and no dog that received meloxicam required rescue analgesia compared to dogs that received a morphine only epidural (31). In another study epidural morphine and systemic carprofen provided superior analgesia for orthopedic pain than carprofen alone (40). Because NSAIDs take at least 7 days to wash out (88) and since our subjects were client owned dogs, ethically we elected to continue their NSAIDs preoperatively and post-operatively. The long wash-out period is also the reason we chose to continue their normal NSAID use during the study. The additional NSAIDs administered to all patients in the present study could have further supplemented analgesia, resulting in similar pain scores among groups. This can also explain why the group which received an opioid only during premedication had similar pain scores and did not require any more rescue analgesia than any other group.

Acepromazine and the analgesic drugs used in this study produce a MAC sparing effect (15, 53). We were unable to show a difference among groups in end tidal isoflurane percentage (ET\textsubscript{Iso}), vaporizer percentage at induction, and vaporizer percentage during the surgical period (Figures 9.5, 9.6). This could be a result of this MAC sparing effect of the drugs used in our study design that equalized the groups’ requirements. The averages for isoflurane vaporizer percentages during the induction (first 15- 20 minutes
on inhalant) phase among groups are typical of isoflurane induction percentages in premedicated dogs (1). The MAC of isoflurane in dogs has been reported to be $1.3 \pm 0.15\%$ to $1.38 \pm 0.08\%$ which is similar to the averages for end-tidal isoflurane concentrations during surgery among groups (1, 16, 29). Acepromazine produces a halothane MAC sparing effect of $45\%$ (53). Literature suggests that the use of MLK co-infusion should reduce MAC-Iso in dogs by $45\%$ (25). Muir et al showed a MAC sparing effect with morphine, lidocaine and ketamine, as well as with MLK co-infusion (25). They found the addition of ketamine and lidocaine did not produce significant MAC sparing effects compared with morphine alone (25). Campoy et al showed that a bupivacaine-morphine epidural reduces isoflurane requirements and mean arterial pressures in dogs (30). MLK co-infusions did not reduce inhalant requirements more than the other groups. The isoflurane vaporizer percentages and $ET_{ISO}$ concentrations during the surgical period were $1.77 \pm 0.53$, $2.03 \pm 0.45$, $1.77 \pm 0.54$, and $1.94 \pm 0.52$ for the MLK group, the LE group, the MLK + LE group and M only group respectively. The $ET_{ISO}$ concentrations were $1.2 \pm 0.4$, $1.5 \pm 0.4$, $1.2 \pm 0.3$, and $1.5 \pm 0.6$. While the groups receiving MLK co-infusion trended towards a lower value, the standard deviations were large and there was no significant difference among groups. All four analgesic protocols we used reduce an intra-operative isoflurane requirement which is probably why we did not see a difference among groups in intra-operative cardiovascular data and anesthetic depth. This project was not designed to be a MAC study comparing the intra-operative
inhalant sparing capacity of each group. A MAC study comparing these 4 groups may have shown a significant difference in intra-operative values. However in our study, dogs were anesthetized and monitored by 4th year veterinary students. Novice anesthetists are not always confident in minimizing vaporizer settings. Their inexperience may have impacted the inhalant requirements we observed among groups. Even so, the lack of MAC sparing effect shown intra-operatively should not have impacted the pain scoring in the post-operative period. It must be noted, as well, that the gas analyzers were not calibrated prior to each anesthetic event. The gas analyzer was calibrated once at the start of the study.

Volatile inhalant anesthetics dose relatedly impact cardiopulmonary function. It is not surprising that the intra-operative values we observed, including HR, RR, SBP, and ETCO$_2$ were not different among groups (*Figure 9.1, 9.2, 9.3, 9.4*). All groups were at similar ET$_{ISO}$ concentrations during the induction and surgical anesthesia period. All dogs were mechanically ventilated during the surgical portion of anesthesia to achieve an ETCO$_2$ between 35 – 45 mmHg. Mechanical ventilation impacts blood pressure due to the associated increased intrathoracic pressure that in turn decreases venous return (1). It is possible that mechanical ventilation limited any difference in SBP among groups. Ketamine, even at low infusion rates, has been shown to increase SBP (25) but we did not find a significant increase in SBP in groups receiving MLK co-infusion, although groups receiving MLK co-infusion trended towards having a higher SBP (*Figure 9.3*). SBP was
measured indirectly with either a doppler or via oscillometry which can be inaccurate (1). In summary we found similar cardiopulmonary changes during the pre-surgical and surgical time periods in all 4 groups.

The same surgeon performed all of the TPLO surgeries and the duration of anesthesia, the duration of surgery and the time to extubation were not different among groups (Table 9.5; Figure 9.8). The recruitment of a single surgeon eliminated the inter-surgeon variability and should have reduced the variability of surgical trauma among groups. Three dogs were eliminated from the study during surgery because of surgical complications that required additional surgical corrections that could have impacted post-operative pain. These dogs were replaced by 3 other dogs in subsequent enrollment. The total surgery time (in minutes, mean ± SD) among groups ranged from 58 ± 7 to 72 ± 25. The mean time (in minutes, mean ± SD) from shutting off the vaporizer to extubation for the MLK group, the LE group, the MLK + LE group and the M only group were 21 ± 15, 16 ± 16, 43 ± 31, and 18 ± 12 respectively. Our results are comparable to a study by Lopez et al (2009) that compared recovery from anesthesia with isoflurane, sevoflurane and desflurane in healthy dogs. In that study mean ± SD time to extubation was 13.0 ± 5.4 minutes for isoflurane. Our times were longer, especially in the MLK groups because of the additional sedation associated with the co-infusion. Groups receiving MLK co-infusion trended towards having a longer extubation time although this finding was not significant. It is possible that a larger experimental number would have indicated
statistical significance in the MLK groups. Clinically we tend to note longer times to extubation in dogs that receive MLK compared to those that do not.

There was no statistical significance among groups in the number of dogs requiring rescue analgesia, time to first rescue analgesia administration, average cumulative dose of rescue analgesia, or average number of rescue analgesia doses (Table 9.6). Within each group some dogs required rescue analgesia at some point in the 24 hour post-operative period. Four of 12 dogs in the MLK group received rescue analgesia. Two of these 4 dogs required rescue analgesia at time 0. One dog in this group required rescue analgesia at 8 of the 10 time points. The LE group had 4 of 12 dogs which received rescue analgesia. Only one of these 4 dogs required rescue analgesia at time 0. The MLK + LE group had 5 of 12 dogs that received rescue analgesia. None of these 5 dogs required rescue analgesia at time 0. The M only group had 3 of 12 dogs which received rescue analgesia. None of these 3 dogs required rescue analgesia at time 0. One dog in the M only group required rescue analgesia at 6 out of the 10 time points. In the groups with an LE included in their protocol, no dog required more than 3 doses of rescue analgesia during the 24 hour post-operative period. When comparing average pain scores at each time period we included all dogs regardless if they received rescue analgesia. Therefore, enough dogs received rescue analgesia early in the study, probably minimizing pain scoring differences among groups. The pain score standard deviations were large in each group at each time point and this probably contributed to finding no difference among
groups. The large standard deviations may have been due to the inclusion of dogs that already received rescue analgesia or due to variation among dogs themselves. Analysis was run after removing all dogs that received rescue analgesia and still found no difference in average pain scores, although the standard deviations appear smaller (Figure 10.1). No group showed a trend in rescue analgesia requirements for either the number of doses or the time to first rescue analgesia administration. Hoelzler et al found that no differences in measured indices of post-operative pain were observed among groups (epidural, intra-articular, and intravenous) but the epidural and intra-articular groups had longer times to first rescue analgesia compared to the control group (74). Differences in our study versus that of Hoelzler et al may be because we used different epidural drugs combinations and drug concentrations. Additionally, Hoelzler et al used 2 pain scoring methods, neither of which has been validated in assessing acute orthopedic pain.
Figure 10.1: Mean pain scores without rescue analgesia
Acepromazine’s duration of action is 4 – 6 hours. This is reflected in our sedation scores during the initial 3 hour post-operative period (Figure 9.10). We chose to independently score pain and sedation in an attempt to not confuse sedation for analgesia. There was no difference in sedation scores among groups throughout the 24 hour post-operative period (Table 9.11, Figures 9.10, 9.11). Sedation scores progressively decreased over time while pain scores did not change suggesting that we assessed pain independently of sedation in each group (Figures 9.13, 9.15). Pain score categories such as attitude and attention to the surgical site might result in lower pain scores in overly sedate dogs, therefore as sedation wore off over time we should have noted that pain scores increased. This was not the case in our study, again indicating good independence of the pain and sedation scoring systems we used. Although sedation and pain were scored independently, it does not mean that sedation and pain scores were not related.

Multiple confounding factors can affect the diagnostic validity of pain scoring (66, 82). These factors include psychological and behavioral status, as well as administration of anxiolytics, narcotics, and other agents. Methods of scoring pain in animals rely on the observer’s interpretation of animal behavior (5, 6, 7, 22, 59, 60, 61, 62, 63, 64). The MGCMPS has been validated for use in dogs with orthopedic pain. It has shown smaller inter-observer variation, and results are less influenced by sedation than other scoring systems (62). Large standard deviations were seen within our groups and consequently this may have contributed to the lack of any differences. The addition of an
alternate pain scoring system may have been more sensitive in detecting differences in pain scores among groups (7, 63, 64). However, other validated pain scoring systems have drawbacks and we did not consider their use during the project design. For example, the University of Melbourne Pain Score (UMPS) system relies on physiological factors such as pupil size, salivation, heart and respiratory rate which are non-specific to pain. Drugs such as morphine can reduce heart rate, alter respiratory rate and produce miosis in dogs (1). Therefore, the administration of morphine as post-operative rescue analgesic in the present study might have influenced subsequent MGCMPS scores.

Neuroendocrine and physiologic changes have been assessed for their correlation to pain. Many pain studies include cortisol measurements (16, 18) in their research design. Certain combinations of analgesia drugs and techniques can lower cortisol values and HR and they have not been correlated with a particular post-operative pain score or level of clinical pain. There are many factors that may impact these neuroendocrine and physiologic changes such as demeanor, pain, dehydration, and concurrently delivered drugs (1).

Study limitations should be addressed. First is the issue of scoring pain in animals. Despite their systematic methodology pain scoring systems are subjective assessments; each with unique limitations. Two observers scored pain and sedation in the present study. The 2 observers practiced pain and sedation scoring of various dogs after TPLOs prior to the start of the project with the objective to decrease inter-observer
variation. The MGCMPS has less inter-observer variability than other pain scoring methods. However, a single observer would have eliminated any variability. The addition of another pain scoring method may have improved sensitivity of pain scoring. Several other studies have included a VAS, an algometer, or von Frey filament measurements along with the MGCMPS. The 4A VET pain scoring method was validated after this project was in progress. The 4A VET system includes physiologic and subjective categories to numerically score pain. This system has been shown pain scores to be influenced less by sedation and can also be applied to a larger variety of surgical causes of pain (soft tissue vs orthopedic). It is also validated in cats as well as in dogs. Retrospectively, the inclusion of another method of pain assessment may have complimented our project.

In our original project design, we calculated power with the intent to show a difference of 2 in pain scores. If we had had calculated power to show a difference of 1 in pain scores, perhaps we would have shown a larger difference in pain scores among groups. This would have required a greater experimental number per each group.

NSAIDs as previously discussed could have minimized pain scores among groups and differences in pain scores among groups. All dogs were receiving an NSAID chronically prior to admission to the study, and all dogs were administered an NSAIDs at extubation. Studies have demonstrated NSAID associated analgesia to be equal or
superior to that of certain opioids. Pain was well control among groups at all time points throughout the study. The highest pain score achieved was 7 out of 24.

The technique of epidural needle placement could have been a confounding factor in data because we had more than 1 person perform the epidurals. Although each of these individuals were trained in the technique, if only one trained person had performed all of the epidurals, there might have been less variability. Some studies used fluoroscopy to confirm epidural placement prior to injection of medications. Confirming epidural needle placement using fluoroscopy or ultrasound guidance would have assured that the epidural space was entered in each dog. Even when epidural needle placement is correct other things can influence epidural drug spread such as the positioning of the dog, anatomic differences unique to each animal, as well as, properties like the baricity of the drugs themselves (1).

Cruciate ligament rupture is often a chronic condition associated with osteoarthritis. Patients with chronic orthopedic issues, such as a torn cruciate ligaments experience chronic pain and possible up-regulation of pain responses. Chronic pain may alter typical pain responses to an acute injury such as cruciate ligament surgery (neuroplasticity).

We have shown that all of our post-operative dogs required frequent monitoring for signs of breakthrough pain regardless of the analgesic technique used which coincides with drug duration of action. Each group had dogs that required rescue analgesia and
each dog that received rescue analgesia had unique rescue analgesia requirements in both numbers of dosages administered and times by which rescue analgesia was required.

It is possible that all protocols used in the present study provide similar pain control because all groups had similar, relatively low average pain scores during the 24 hour post-operative period. These 4 protocols are all commonly used at OSU VMC and other institutions for pain control for various orthopedic procedures. Perhaps, if we followed these dogs for a longer period of time post-operatively, we would have found statistical significance in long-term analgesic requirements. However, our study was designed to compare analgesia in the 24 hour post-operative period. From our data, we can conclude that all 4 techniques provide similar, effective analgesia and sedation for 24 hours post operatively.
References


50. Web resource: Local anaesthetics and additive drugs.


71. Manchikanti L, Damron KS, Rivera JJ, McManus CD, Jackson SD, Barnhill RC, Martin JC. Evaluation of the effect of sedation as a confounding factor in the


Appendix A: Modified Glasgow Composite Measurement Pain Score System

Dog's name_________________________ Hospital number_______________ Date____________
Time_____________________________ Procedure____________________________________

A. Look at dog in kennel

<table>
<thead>
<tr>
<th></th>
<th>(i)</th>
<th>(ii)</th>
<th>(iii)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quiet</td>
<td>Ignoring any wound, painful area</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Crying or whimpering</td>
<td>Licking, looking or rubbing it</td>
<td>Hunched/tense</td>
</tr>
<tr>
<td></td>
<td>Groaning</td>
<td>Chewing it</td>
<td>Rigid</td>
</tr>
<tr>
<td></td>
<td>Screaming</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For clinical reasons it may not be possible to carry out question B. Please tick if this is the case and then proceed to C.

B. Put lead on dog and lead out of kennel

When the dog rises/walks is it?

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Lame</th>
<th>Slow reluctant</th>
<th>Stiff</th>
<th>It refuses to move</th>
</tr>
</thead>
<tbody>
<tr>
<td>(iv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C. If it has a wound/painful area apply gentle pressure 2 inches round the site

Does it?

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Lame</th>
<th>Slow reluctant</th>
<th>Stiff</th>
<th>It refuses to move</th>
</tr>
</thead>
<tbody>
<tr>
<td>(v)</td>
<td>Do nothing</td>
<td>Flinch</td>
<td>Growl/guard area</td>
<td>Snap</td>
<td>Cry</td>
</tr>
</tbody>
</table>

D. Overall

Is the dog?

<table>
<thead>
<tr>
<th></th>
<th>Happy and content/happy and bouncy</th>
<th>Quiet or indifferent</th>
<th>Aggressive</th>
<th>Nervous/anxious/fearful</th>
<th>Depressed/uninterested</th>
</tr>
</thead>
<tbody>
<tr>
<td>(vi)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Is the dog?

<table>
<thead>
<tr>
<th></th>
<th>Happy and content/happy and bouncy</th>
<th>Quiet or indifferent</th>
<th>Aggressive</th>
<th>Nervous/anxious/fearful</th>
<th>Depressed/uninterested</th>
</tr>
</thead>
<tbody>
<tr>
<td>(vii)</td>
<td>Comfortable</td>
<td>Uncomfortable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix B: Sedation Scoring System

<table>
<thead>
<tr>
<th>Observation</th>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vocalization</td>
<td>0</td>
<td>Quiet</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>Whining softly but quiets with soothing touch</td>
</tr>
<tr>
<td></td>
<td>-2</td>
<td>Whining continuously</td>
</tr>
<tr>
<td></td>
<td>-3</td>
<td>Barking continuously</td>
</tr>
<tr>
<td>Posture</td>
<td>3</td>
<td>Lateral recumbency</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Sternal recumbency</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Sitting or ataxic</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Standing</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>Continuous movement</td>
</tr>
<tr>
<td>Appearance</td>
<td>3</td>
<td>Eyes sunken, glazed, unfocused, ventromedial rotation</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Eyes glazed but follow movement</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Nictitating membrane protruded; normal visual response</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Normal appearance</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>Pupils dilated; abnormal facial expression</td>
</tr>
<tr>
<td>Interactive</td>
<td>3</td>
<td>Recumbent; no response to voice or touch</td>
</tr>
<tr>
<td>Behaviors</td>
<td>2</td>
<td>Recumbent; lifts head in response to voice or touch</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Recumbent but rises in response to voice or touch</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Standing or sitting up; normal response to voice or touch</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>Moves away from voice or touch (&quot;jumpy&quot;)</td>
</tr>
<tr>
<td></td>
<td>-2</td>
<td>Growls/hisses when approached or touched</td>
</tr>
<tr>
<td></td>
<td>-3</td>
<td>Bites/swats when approached</td>
</tr>
<tr>
<td>Restrainability</td>
<td>2</td>
<td>Lies on floor with minimal restraint needed</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Lies of floor with light restraint of head/neck</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Sits up on floor; attempts to jump despite restraint</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>Struggles against restraint continuously</td>
</tr>
<tr>
<td></td>
<td>-2</td>
<td>Cannot be restrained for &gt; 20 seconds</td>
</tr>
<tr>
<td>Noise response</td>
<td>3</td>
<td>No response to a hand clap near the head</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Minimal response to a hand clap near head</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Slow/moderate response to a hand clap near head</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Brisk response to a hand clap; raises head, eyes open</td>
</tr>
</tbody>
</table>