DISSERTATION

PERIANESTHESIA ANALGESIA, RECOVERY EFFICACY, AND FINANCIAL IMPACT OF ULTRASOUND-GUIDED LUMBAR PLEXUS AND SCIATIC NERVE ANALGESIA IN DOGS UNDERGOING TIBIAL PLATEAU LEVELING OSTEOTOMY

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ABSTRACT

PERIANESTHESIA ANALGESIA, RECOVERY EFFICACY, AND FINANCIAL IMPACT OF ULTRASOUND-GUIDED LUMBAR PLEXUS AND SCIATIC NERVE ANALGESIA IN DOGS UNDERGOING TIBIAL PLATEAU LEVELING OSTEOTOMY

Perioperative analgesia is critical for patients undergoing surgery because uncontrolled pain can result in deleterious consequences and predispose chronic pain. Therefore, developing an appropriate analgesia technique is crucial, and in this study, an analgesia protocol was investigated in dogs undergoing tibial plateau leveling osteotomy (TPLO). The TPLO is a surgical technique used to stabilize the stifle joint for treating cranial cruciate ligament disease. This surgical procedure is invasive and painful. Therefore, multimodal analgesia is often required for controlling pain associated with TPLO surgery. This study used ultrasound-guided regional anesthesia of the lumbar plexus and sciatic nerve as a component of multimodal analgesia to control perioperative pain compared to patients only receiving a standard systemic analgesia. The study was designed to evaluate the efficacy of regional anesthesia and to determine the financial impact of this additional multimodal procedure. We hypothesized that ultrasound-guided lumbar plexus and sciatic nerve blocks would provide a better analgesic effect intraoperative and postoperatively. The second part of the study we hypothesized that ultrasound-guided lumbar plexus and sciatic nerve blocks would increase the anesthesia cost. It would then be possible to determine a cost – benefit of the procedure.

The study was designed as a prospective, randomized, blinded clinical trial. Twenty dogs underwent TPLO surgery were enrolled in the study and randomly assigned to regional analgesia (RA) or control (CON) group. Dogs in the RA group received 0.5% ropivacaine for ultrasound-guided lumbar plexus and sciatic nerve blocks. The total dose of ropivacaine for both blocks was 0.15 mg/kg. Dogs in the CON group received sterile 0.9% saline for the blocks. All dogs received 0.2 mg/kg of hydromorphone and 0.02 mg/kg of atropine for anesthesia premedication. Propofol was administered for anesthesia induction to perform endotracheal tube intubation. Isoflurane in oxygen was delivered using a circle rebreathing

system to maintain anesthesia. The ultrasound-guided lumbar plexus and sciatic nerve blocks were performed prior to TPLO surgery. Fentanyl was used for intraoperative as rescue analgesia to reduce the response from surgical stimulation or with an increase in heart rate, respiratory rate, or mean arterial blood pressure. Isoflurane was adjusted to maintain the appropriate anesthesia plane. Hypotension was treated following a stepwise protocol, in a sequencing fashion. The treatment protocol was added until the complications was resolved. The treatment protocol started from decreased isoflurane vaporizer setting, lactate Ringer's solution bolus, hetastarch bolus, and dopamine administration. At extubation, the recovery quality and pain were evaluated. Dexmedetomidine was used to treat poor recovery quality and pain. During the postoperative 12 hours period, pain and recovery quality were assessed by Colorado State University acute pain scale, visual analog pain scale, and modified University of Melbourne pain scale. Fentanyl or methadone was used for postoperative rescue analgesia. Dexmedetomidine or acepromazine was administered to calm the patient. The amount of every drug used, complications management, and extra nursing care were recorded to evaluate the blocks' efficacy. The micro-costing technique was used to collect the financial data and was analyzed to determine the financial impact.

In the clinical study, there was a statistically significant difference in the amount of intraoperative fentanyl administered for rescue analgesia between the groups ($p = 0.02$), with lesser doses given to the RA group. Hypotension was found in 40% of dogs in the RA group and 80% of the dogs in the CON group ($p = 0.16$). Dogs in the RA group required less intensive treatment than in the CON group. There was a statistically significant difference in the recovery scores between the groups, with those in the RA group having lower recovery scores ($p = 0.04$). In the postoperative period, the time to receive the first dose of rescue analgesia for dogs in the RA group was longer than dogs in the CON group ($p=0.04$).

Micro-costing method was used for collecting the monetary information. The cost analysis was performed for evaluating the costs of dogs that received ultrasound-guided regional anesthesia with 0.5% ropivacaine and 0.5% sterile saline. The anesthesia fixed cost for the surgery was US$354. There was a statistically significant difference between the variable costs, with the RA group (US$82.65 (69.15-94.56); median (min-max)) having less anesthesia variable costs than dogs in the CON group (US$125.8 (55.23 to

156.35); $p = 0.02$). The additional cost for a charge per service of the use of ultrasound and electro-nerve stimulator machines (US$26.62) affects the total anesthesia cost for the RA group into both direction, it can enhance and save the total anesthesia cost. It can increases the total anesthesia cost by $US40.54 per dog and it can save the total anesthesia cost by $US35.17 per dog. From the clinical perspective, the number of dogs receiving TPLO surgery at the study hospital is approximately 160 cases per year. This number was used for estimating cost benefit per year performing nerve blocks for TPLO surgery and found that the nerve blocks would potentially increase the total cost for 160 dogs to US$6,486.40 per year but would decrease the total anesthesia cost by US$5,627.20 per year.

Ultrasound-guided lumbar plexus and sciatic nerve regional analgesia was found to be an effective multimodal analgesia for TPLO surgery. The technique provided effective intraoperative analgesia that decreased rescue analgesia during surgery and led to better recovery from anesthesia for the dogs in this study. The ultrasound-guided analgesia technique would increase anesthesia costs but better analgesia, anesthesia, and decreased complications provided significant cost-saving benefits when performing regional analgesia for TPLO surgery.

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CHAPTER 1: PAIN IN VETERINARY MEDICINE

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (IASP Task force on taxonomy 1994). Therefore, pain is an integration of conscious experience that involves not only nociception but also one's sensation. Nociception is a neural process that encodes noxious stimuli into a nociceptive signal and transmits the modulated signal to the brain for integrating impulse information (Hudspith 2016). Human and animal studies have shown that the nociceptive sensation can be modified by experiences, such as fear, memory, and stress, which can potentiate or decrease the sensation of pain (Vidal & Jacob 1982; Huang et al. 2011; Ahmad & Zakaria 2015). Pain sensation manifests a grading response which consists of the withdrawal of a body part (withdrawal reflex), changes in autonomic response, and activation of the hypothalamic pituitary axis that increases stress response hormones. (Wilmore 2002; McGregor et al. 2003; Bomholt et al. 2004; Ledowski et al. 2012) This grading reaction is also shown in terms of a behavioral response that can induce self-trauma, altered sleep habits, movement, grooming, and socialization; changes in intestinal function; and a prolonged recovery time from underlying disease and surgery (Holton et al. 2001; Crook 2014). These deleterious consequences can be alleviated by effective pain management that results in a better wound healing process, a decreased length of hospitalization, and improved quality of life (Yoost Timothy R et al. 2009; Farag et al. 2013; Matsuzaki & Upton 2013). To provide effective pain management, it is necessary to understand pain physiology, pain management concepts, and modalities to treat pain. These details are discussed in this chapter.

1.1 Physiology of nociception

The nociceptive pathway is a multistep process that includes transduction, transmission, modulation, and perception (Mertens et al. 2015). The process starts from the periphery, where stimuli activate receptors, and nociceptive signals travel to the brain.

Transduction occurs when intense thermal, chemical, or mechanical stimuli reach the noxious range to the point that nociceptors are excited. The high threshold of nociceptors is essential for differentiating between injured stimuli and innocuous sensations. Nociceptors are a subpopulation of peripheral nerve fibers. The cell body of the neuron is situated in the dorsal root ganglion and trigeminal nerve ganglion, with peripheral axons that branch to innervate target tissue and central axons that reach the spinal cord. The peripheral terminals of nociceptors are free nerve endings where specific noxious receptors are located (Basbaum et al. 2009; Shilo & Pascoe 2014). Noxious receptors are specific to nociceptive stimuli, and their activation can be modulated by other factors or mediators.

Thermal nociceptive stimuli can be detected by specific receptors. High temperature can be detected by receptors in the transient receptor potential (TRP) family. TRP is a six transmembrane protein that acts as a non-selective ion channel. TRPV1 can detect high temperatures above 42°C by sensitizing the receptor at the C-terminus and allowing the ion channel to open. An influx of calcium into the neuron stimulates nearby voltage-gated sodium channels to generate an action potential. Activation of the TRPV1 receptor can be modulated by several agents due to the structure of the receptor, which has various phosphorylation sites and proton receptor sites. Proinflammatory mediators such as prostaglandin upregulate the phosphokinase A pathway and augment the activity of TRPV1 in neurons. Other proinflammatory stimuli, such as adenosine triphosphate (ATP), bradykinin, trypsin, and tryptase, activate Gq-coupled receptors via phosphokinase C to decrease the temperature threshold for TRPV1 activation. Protons can initiate TRPV1 activity by binding to the proton-active gate that resides on the extracellular area of the molecule. Therefore, TRPV1 can be activated by nociceptive high-temperature stimuli and can also be sensitized by acid or inflammatory agents (Rosenbaum T & SA. 2007; Julius 2013; Armstrong SA & MJ. 2020). Another receptor from the TRP family sensitized by noxious, cold temperatures is TRPM8. This receptor has a temperature threshold of 8-15ºC (Julius 2013; Mickle et al. 2015). The cold temperature threshold of TRPM8 is fine-tuned by coordinated effects from two-pore potassium channels (K_{2P}) (Basbaum et al. 2009). Differences in the temperature ranges of nociceptive stimuli are detected mainly by

TRP superfamily receptors, but these receptors are not limited to stimulation by only thermal changes. Other mediators can also sensitize the receptors.

Chemical nociceptive stimuli from ischemic or inflammatory processes can activate TRPA1 receptors (Julius 2013; Premkumar & Abooj 2013). Inflammatory factors such as bradykinin and ATP activate TRPA1 by pathway-dependent G_q-PLC-coupled receptors and allow the channel to open for ion influx (Julius 2013; Armstrong SA & MJ. 2020). The acid-sensing ion channel (ASIC) is another chemical receptor activated by extracellular protons. These protons stimulate the receptor to allow the cation channel to open and depolarize. This receptor is found in several places in the central and peripheral nervous systems. It is used to detect acids from various etiologies, such as ischemia, inflammation, and even muscle pain due to the release of lactic acid. These various chemicals can stimulate chemical nociceptive receptors mostly to respond to inflammation, infarction, or any extracellular acid production that may harm tissue (Armstrong SA & MJ. 2020).

Mechanical nociceptor impulses have not been able to be definitively characterized. Several receptors are considered mechanical nociceptors, such as TRPV4, Kv1.1 channel, and Piezo protein. TRPV4 is one of TRP family. It can be sensitized by mechanical and osmotic stimuli and playing a role in mechanical hyperalgesia. Kv1.1 is a potassium channel that can be activated mainly by depolarizing changes in membrane potential. The Kv1.1 channel can also be activated gradually by increasing mechanical stimuli. Piezo protein is a non-selective cation channel. It can be sensitized by noxious mechanical stimuli (Basbaum et al. 2009; Eijkelkamp et al. 2013; Julius 2013; Premkumar & Abooj 2013; Gu & Gu 2014). Little is known about these mechanonociceptors, and further study of this group of receptors is needed.

Nociceptors are distributed differently in different body locations. The skin consists of nociceptors that specifically respond to high or low temperatures, mechanical stimuli, and chemical stimuli. Moreover, there are polymodal receptors in this area that can be activated by more than one nociceptive stimulation. The action potential from polymodal receptors tend to be conveyed by a slow speed nerve fiber (Lynn et al. 1995). At the joint, the majority of the nociceptors are high threshold mechanical and silent nociceptors.

The silent nociceptor in the joint is mechano-insensitive under normal conditions. When the joint becomes inflamed, the nociceptive threshold of the silent nociceptor decreases. The nociceptor is activated both from mechano-innocuous and noxious stimulation. The normal movement of the joint stimulates the nociceptor and causes pain (Schaible 2007). Visceral pain has high threshold nociceptors for chemical mechanical, and thermal stimuli. Polymodal nociceptors and silent nociceptors are commonly found in the visceral organs. The low-density nociceptors in the visceral organs and the insufficiency of the separate visceral sensory pathways in the spinal cord and brain leads to poor localization of the origin of pain. (Giamberardino & Vecchiet 1997; Cervero 2014; Gebhart & Bielefeldt 2016).

The transmission process is when nociceptive nerve fibers convey nociceptive impulses to neurons in the spinal cord. Nociceptors respond to stimulation by opening the central conduction pore of the channel gate, allowing the influx of Na^+ and Ca^{2+}, with a preference for Ca^{2+} influx by three- to nine-fold. This influx results in neuronal plasma depolarization activating voltage-gated sodium channels (Na_v) or voltage-gated calcium channels (Ca_v) to facilitate action potentials and generate nociceptive impulses (Julius 2013; Mickle et al. 2015). The voltage-gated sodium channel is the major channel that initiates and conveys nociceptive information. There are two types of voltage-gated sodium channels (Na_v): tetrodotoxin (TTX)-sensitive channels (TTX-S Na^+) and TTX-resistant channels (TTX-R)., TTX-S Na^+ include $Na_v1.1$, 1.6, and 1.7, and TTX-R include $Na_v1.8$ and 1.9. TTX-S Na^+ channels are activated and inactivated rapidly, while TTX-R Na^+ channels are activated and inactivated at a slower rate. $Na_v1.7$ is activated from small depolarizations and causes Na^+ influx; this influx increases the membrane potential to make it prone to sensitization $Na_v1.8$, which resides in only sensory neurons, particularly nociceptive neurons, has a higher sensitization threshold and requires a greater depolarization voltage to open the channel. Therefore, pre-depolarization from $Na_v1.7$ can help make $Na_v1.8$ more sensitive. The influx of Na^+ from $Na_v1.8$ is crucial for an upstroke in the action potential. $Na_v1.9$ conducts a persistent influx of Na^+ at the subthreshold voltage but does not cause an upstroke for action potentials. During inflammation, the mRNA of the protein for $Na_v1.7$ is synthesized at a higher rate than normal. The $Na_v1.8$ current is increased in response to proinflammatory mediators (adenosine, endothelin, NGF, prostaglandin E_2, serotonin, and tumor necrosis factor-α), and $Na_v1.9$ is prone

to be sensitized by proinflammatory mediators (Schaible et al. 2011). Each Na_v channel has a role to generate action potentials and can be sensitized to increase the activity that enhances nociceptive impulses.

Nociceptive impulses are transmitted at a speed between 0.5 and 200 m/sec. The wide range of conductance speeds is associated with the diameter and presence of a myelinated sheath surrounding some nerve fibers. The diameter range of the fibers is between 0.5 and 20 μm, and the higher the diameter is, the faster the speed. The myelinated sheath allows a greater speed impulse. There are two major classes of afferent fibers that transmit nociceptive signals. Aδ fibers with a medium-sized diameter and covered with a myelinated sheath. Transmission is fast and provides so-called fast or first pain. There are two types of Aδ fibers. Type I Aδ fibers include chemically and mechanically sensitive receptors and high-threshold heat receptors. The threshold of these receptors is reduced when surrounded by injured tissue, which makes the receptors more sensitive. Type I Aδ fibers tend to convey the fast pain of a pinprick or intense mechanical stimuli. Type II Aδ fibers, on the other hand, include heat-sensitive and high-threshold mechanical receptors. The first pain that type II fibers convey is heat pain (Basbaum et al. 2009). The second type of nociceptive afferent fibers are C fibers, which have a small diameter and do not have a myelinated sheath. These C fibers convey slow or secondary pain. The majority of C fibers are from polymodal receptors that respond broadly to several noxious stimuli and other innocuous stimuli (Lemke 2004; Fox 2014a). These afferent fibers are more prone to be sensitized by inflammation. C fibers convey nociceptive stimulation information and other types of information, including cooling sensations, innocuous stroking of the hair, or an itching response. C fibers can be classified into peptidergic and nonpeptidergic fibers. Peptidergic C fibers primarily convey heat or cold nociceptive impulses, while nonpeptidergic C fibers mainly convey mechanical nociceptive impulses. Aβ fibers are large-diameter myelinated fibers with less involvement in pain transmission. The fibers transmit information from normal innocuous stimuli, including vibration, skin and muscle stretching, pressure, stroking, and joint proprioception (Basbaum et al. 2009). Each type of fiber delivers specific information with different speeds to the dorsal horn.

Nociceptive impulses that are transmitted via nerve fibers and reach the dorsal horn have an exact place in the lamina to synapse with second-order neurons in the dorsal horn. Second-order neurons in the dorsal horn of the spinal cord in lamina I receive nociceptive impulses from Aδ and C fibers, second-order neurons in lamina III receive innocuous impulses from Aβ fibers, and second-order neurons in lamina V receive both noxious (Aδ fiber) and innocuous (Aβ fiber) impulses. Neurons in the spinal cord that receive only nociceptive impulses are called nociceptive-specific neurons. Neurons that receive a broad range of impulse intensities located in lamina V are called wide dynamic range (WDR) neurons (Basbaum et al. 2009). These neurons play a role in referred pain, which is characterized by feelings of pain at a site distant from the original location (Basbaum et al. 2009; Murray 2009). Each type of nociceptive stimulus is transmitted by its specific nerve fiber to synapse with a second-order neuron at a particular lamina in the spinal cord before the impulse is sent to the brain.

Modulation is when a pain signal is altered in the body along its pathway of transmission to the brain for pain sensation. The nociceptive signal can be facilitated or inhibited, leading to hyperalgesia or analgesia, respectively (Kirkpatrick et al. 2015). The modulation process can develop in the peripheral and central nervous systems (Basbaum et al. 2009) In the peripheral nervous system, damaged cells release endogenous factors sensitizing the peripheral nervous system. Endogenous factors include neurotransmitters, peptides (substance P, CGRP, bradykinin), neurotrophins, cytokines, chemokines, proteases, protons, eicosanoids and related lipids (prostaglandin, thromboxanes leukotrienes, endocannabinoids). Activated migrated cells include basophils, platelets, neutrophils (IL-1, IL-6, and TNF-α), endothelial cells, keratinocytes, fibroblasts, macrophages, and mast cells. These endogenous factors and activated cells are the so-called inflammatory soup that enhances the inflammatory response and production of pro-algesic agents (prostaglandins, NGF, bradykinin, and extracellular protons). The inflammatory soup lowers the nociceptive threshold of nociceptors so that they are sensitized at lower levels of nociceptive stimuli and are prone to generate action potentials (Basbaum et al. 2009; Mifflin & Kerr 2014; Shilo & Pascoe 2014).

Peripheral sensitization increases pain sensation from a normal level of stimulation, which is evoked at the injury site, called primary hyperalgesia. This hyperalgesia can also be elicited by other nociceptive stimuli such as thermal and mechanical stimuli (Raja et al. 1988; Cervero et al. 2003).

In the central nervous system, modulation can occur in both the spinal cord and brain. The common modulation process involves three major mechanisms: N-methyl-D-aspartate (NMDA) receptor-mediated hypersensitivity (a wind-up mechanism), tonic inhibitory control, and glial-neuronal interaction (Basbaum et al. 2009). NMDA receptor-mediated hypersensitivity or the wind-up mechanism is associated with alterations in the glutaminergic neurotransmission system. In acute pain, glutamate is released from C fibers in the presynaptic area as a neurotransmitter to transmit nociceptive signals to second-order neurons. Glutamate acts on the amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor and generates an action potential. In this situation, the NMDA receptor is not activated and stays in the silent stage. Once high-intensity pain or peripheral sensitization results in a chronic, intense nociceptive signal sent to a first-order neuron, glutamate and substance P (SP) are released in large amounts. The release of SP together with calcitonin gene-related peptide (CGRP) from a first-order neuron with profound activation of AMPA receptors generates high-intensity depolarization. This high-intensity depolarization removes Mg^{2+}, which tonically suppresses NMDA receptors. Once Mg^{2+} is removed and glutamate is associated with the binding sites of NMDA receptors, there is an influx of Ca^{2+}, thus activating several intracellular pathways and initiating the hyperexcitability of second-order neurons as a part of central sensitization (Shilo & Pascoe 2014). The increasing Ca^{2+} concentration from the wind-up mechanism elicits an action potential together with phosphorylation activity. Phosphorylation activates several sensitization mediators, such as protein kinase K (PKC), phosphokinase A (PKA), extracellular signal-regulated kinase (ERK), and calcium/calmodulin-dependent protein kinase type II (CaM-KII). These activated mediators change the threshold and activation kinetics of NMDA and AMPA receptors, boosting synaptic efficacy. ERK also phosphorylates potassium voltage channel 4.2 to decrease the K^+ current and enhance membrane excitability. PKA, CaM-KII, and ERK promote vesicles that store metabotropic glutamate receptors (mGluRs) and AMPA receptors under the synapse area to the postsynaptic membrane. ERK, together with

cAMP response element binding protein (CREB), drives the transcription of c-*Fos*, tyrosine kinase B, and cyclooxygenase-2 (COX-2), which are factors that maintain central sensitization (Latremoliere & Woolf 2009).

The next modulation process originates from the brain and provides tonic inhibitory control to second-order neurons in the spinal cord. Modulation from the perception area of the brain or descending inhibitory monoaminergic pain pathway involves the periaqueductal gray (PAG), which resides in the midbrain and receives impulses from the supraspinal center and spinal cord (Fox 2014a). The PAG has two types of location-specific activation that act in response to pain. The ventrolateral area of the PAG induces long-acting and opioid-mediated analgesia, which causes passive coping or a conservation-withdrawal reaction. The results of this action are responses to extreme, inescapable physical stress and traumatic injury, and this action promotes recovery and healing. Another area resides in the dorsolateral and lateral areas of the PAG; this area provides a short-acting and nonopioid-mediated response to pain that causes an active-coping or defensive reaction. After activation, serotonin is released into the dorsal horn of the spinal cord, activates the interneuron to release enkephalin or dynorphin to bind to μ opioid receptors. The activation of the μ opioid receptor inhibits the first-order neuron to release of substance P and resulting in inhibit second-order neuron activation, and the pain signal is inhibited. This inhibition process is commonly found in C fibers rather than Aδ fibers (Fox 2014a; Shilo & Pascoe 2014). Another type of modulation occurs via the pontine noradrenergic system, which is influenced by neurons in the rostral ventromedial medulla (RVM) (Bourne et al. 2014). The locus coeruleus and other nuclear groups in the A5 and A7 regions of the pons release norepinephrine into the spinal cord, which acts on α_2 adrenoceptors to inhibit the transmission of nociceptive impulses by presynaptic and postsynaptic neurons (Bourne et al. 2014). This descending inhibition from the brain that affects the spinal cord and is mediated by serotonin and the norepinephrine system is the so-called descending monoaminergic pathway (Kwon et al. 2014). The imbalance of this descending monoamine pathway is involved in central sensitization. The serotonergic pathway can activate or decrease nociceptive responses depending on whether the pain is acute or chronic respectively. In the chronic phase, the nociceptive mediators in the pathway facilitate and enhance

mechanical activation and pronociceptive effects in the dorsal horn. These may disrupt the norepinephrine pathway, descending inhibition of the nociceptive mechanism is diminished (Kwon et al. 2014).

Another process involved in tonic inhibition control is associated with the loss of GABAergic and glycinergic inhibitory interneuron function. Interneurons are distributed in the superficial dorsal area with a crucial function in the gate control theory of pain. Loss of interneuron function, which is called disinhibition, enhances the nociceptive impulse that a second-order neuron transmits to a third-order neuron. Disinhibition can be involved in the death of GABAergic interneurons, which manifest from high-intensity signals of injured peripheral neurons (Basbaum et al. 2009). Loss of tonic inhibition in the spinal cord results in the continued generation of nociceptive signals, consequently contributing to central sensitization.

The modulation of glial-neuronal interactions involves microglia and astrocytes. In the central nervous system, the cells involved are resident macrophages. Microglia migrate to either the dorsal horn of the terminal area or the ventral horn of the neuron whose axon is damaged. This sentinel cell releases inflammatory mediators, which enhance central sensitization and persistent pain. Astrocytes reside in surrounding synapse areas to nourish neurons and regulate the external chemical environment during synaptic transmission. They can be activated by tissue or nerve damage, but their activation is delayed and persists longer than that of microglia. These cells do not induce but maintain central sensitization (Ji et al. 2013; Chapman & Vierck 2017). Glial-neuronal interactions are activated via inflammatory mechanisms and tend to maintain the dynamics of central sensitization.

Modulation is a process that occurs in several areas of the nociceptive pathway. In the area where transduction is processed, peripheral sensitization may increase the intensity and frequency of the nociceptive signal that is carried to the dorsal horn. A large nociceptive signal can result in the development of the wind-up mechanism and can cause central sensitization. Moreover, in the dorsal horn of the spinal cord, descending inhibition signals from the supraspinal area prevent an ascending nociceptive signal. Once the descending pain pathway from the brain to the dorsal horn is disrupted or if chronic pain develops, all nociceptive signals are relayed to the perception area of the brain. Glial cells and astrocytes enhance central

sensitization via an inflammatory mechanism. Therefore, modulation involves both the inhibition and facilitation of nociceptive signals, which can be found along the nociceptive pathway.

Nociceptive impulses derived from spinal cord dorsal horn neurons are transmitted to different regions of the brain. Perception regions receive signals from various pathways, mainly via the spinothalamic tract (STT), spinoreticular tract (SRT), and spinohypothalamic tract (SHT). The names of the tracts are based on their origin and the perception area of the tract. The spinothalamic tract originates in lamina I and deeper laminae and synapses in the contralateral thalamus. The thalamus relays the noxious information to 1) the SI somatosensory cortex, where the nociceptive impulse intensity and origin of the location are encoded; 2) the SII somatosensory cortex, where painful events are recognized, learned and memorized, and the nociceptive signal is relayed to limbic structures in the temporal lobe; 3) the insular cortex, where autonomic responses to noxious stimuli are integrated; and 4) the anterior cingulate gyrus, where pain and emotion are interconnected, allowing the output of pain in this region to command an immediate behavioral response (Meintjes 2012). The spinoreticular tract has third-order neurons that reside in the reticular formation of the brainstem, with a portion of neurons that travel to the thalamus. Neurons in the reticular formation respond to emotional reactions, such as depression, anxiety, and suffering. Moreover, sleep and consciousness are also associated with the reticular formation. The spinohypothalamic tract is associated with third-order neurons in the hypothalamus of the forebrain. After receiving a nociceptive impulse, the response of this area is involved in neuroendocrine and autonomic responses to stress (Fox 2014a).

1.2 Pain classification

There are two major classifications for pain: acute and chronic pain. The specific characteristics of each type of pain are associated with the cause, mechanism, duration, and function, providing distinctive consequences and treatments. An overview of both classes of pain is provided in the following section.

1.2.1 Acute pain (Adaptive pain)

Acute pain is a warning signal for bodily harm. It triggers avoidance, such as the fight or flight response to stimuli. This type of pain is perceived via noxious stimuli (chemical, mechanical, and

temperature) via nociceptors. The impulse is transmitted to second-order neurons in the central nervous system, and the nociceptive signal is perceived by third-order neurons. This somatic nociceptive signal provides information regarding the intensity, location, and duration of pain (Kehlet et al. 2006). This acute pain is a protective biological function that decreases behaviors that cause risk and promotes tissue healing (Chapman & Vierck 2017). However, during trauma or when performing surgery, acute pain can be harmful. It creates a stress-emotional response, predisposes to a catabolic state that increases O2 consumption, triggers compensatory mechanisms such as muscle spasms, creates an endocrine response, and leads to neuronal changes that could lead to chronic pain. Preventing and treating acute pain is essential to prevent the development of chronic pain, and it is an ethical commitment to maintaining the quality of life (Fox 2014a).

1.2.2 Chronic pain

Chronic pain is defined by the IASP as "pain without apparent biological value which has persisted beyond normal tissue healing time" (Hudspith 2016). It is pain that develops without any benefits (Belshaw & Yeates 2018). Chronic pain is difficult to treat because it requires a multidisciplinary approach to resolve conditions that include both medical and nonmedical therapy (MacFarlane et al. 2014). It is difficult to detect in animals due to the different etiologies underlying the condition (Lascelles et al. 2019; Monteiro & Steagall 2019). Chronic pain can develop in several conditions, such as osteoarthritis, cancer, neuropathies, and surgery (Belshaw & Yeates 2018).

Surgery results in pain due to mechanical nociceptive stimulation, inflammatory processes, and nerve damage. Mechanical noxious signals are generated due to surgical incisions and traumatized tissues (Brennan 2011). Inflammation results from tissue handling. The damaged tissue releases inflammatory mediators to activate nociceptors. Typically, this acute inflammatory reaction is resolved following the wound healing process. Cases, where the wound has pathogen contamination, cases where foreign materials exist at the site, or cases with any cause that delays wound healing or results in persistent inflammation, may be predisposed to the development of chronic surgical pain (Chapman & Vierck 2017). Another factor that causes surgical pain is nerve damage, which cannot be avoided during surgery. Two possible

consequences may result from nerve damage. First, the nerve might lose its transmission capacity to send nerve impulses. Second, the nerve might develop abnormal neural function, inducing hypersensitization (Kehlet et al. 2006). This hypersensitization from nerve injury is called ectopic afferent nerve activity. It generates action potentials in afferent nociceptive pathways caused by subthreshold oscillations in the resting membrane potential. This lower threshold generates rhythmic depolarization without proper nociceptive stimuli (Moore 2016). The inflammatory response and nerve damage can cause peripheral sensitization, which provides abnormal dynamic nociceptive stimulation and an ongoing maintenance pain state. These carry-on nociceptive signals may elicit wind-up mechanisms, which are part of central sensitization. Moreover, diminished descending inhibitory processes and glial cell activities are crucial factors for developing central sensitization and, consequently, the cause of chronic pain (Kehlet et al. 2006; Fox 2014a). Chronic surgical pain in animals leads to poor surgical outcomes and causes perioperative complications, such as decreased exercise tolerance; difficulty standing, walking, or any physical motion; reduced sociability and play behavior; and increased self-trauma of the surgical site (Epstein et al. 2015; McCally et al. 2015; Belshaw & Yeates 2018). As a result, acute surgical pain management is essential for preventing chronic pain development and its harmful consequences. (Kehlet et al. 2006).

1.3 Pharmacological options for analgesia

Pain management includes nonpharmacological and pharmacological options. The nonpharmacological techniques commonly used to relieve pain include acupuncture, physical rehabilitation, and thermal modification. Currently, the use of nonpharmacological analgesic modalities offer limited benefits for pain management. Nonpharmacological modalities are recommended in addition to treatment plans with pharmacological techniques as a mainstay approach. The pharmacological options rely on drugs that bind to receptors or ion channels that increase the nociceptive threshold either at the level of the nociceptors, transmission fibers or CNS processing centers. To manage surgical pain, there are several drugs and application techniques to treat perioperative pain. Preventive analgesia is a technique that consists of pre-emptive, intraoperative, and postoperative analgesia. Pre-emptive analgesia is a strategy that provides analgesic intervention before surgery, for example, the use of local anesthesia that can prevent the

conveyance of nociceptive signals. It is considered by some authors that pre-emptive techniques provide better analgesia than the same intervention given during or after surgery. The decreased afferent nociceptive input may decrease the possibility of central sensitization. However, pre-emptive analgesia may not be sufficient for complete analgesia. Analgesia management during the preoperative period concomitant with intraoperative and postoperative periods shows better analgesic efficacy for adequate pain management. The time of providing analgesia is crucial, but effective modalities and techniques are also important; thus, multimodal analgesia plays a part in this analgesia strategy (Dahl & Kehlet 2011). Multimodal analgesia is a technique that employs more than one analgesia modality to act along nociceptive pathways. The combination of various analgesic drugs and techniques allow modulation of the pain pathway by synergistic analgesic effects that enable the practitioner to use a lower dose of drugs, resulting in decreased adverse effects. Each analgesic drug has its pharmacological properties that act on a different level of the nociceptive pathway, allowing the clinician to induce analgesia by targeting different portions of the pain pathway (Gritsenko et al. 2014; Polomano et al. 2017). Surgical pain management with perioperative and multimodal analgesic techniques is considered the gold standard to prevent and treat surgical pain. The common pharmacological options for perioperative and multimodal analgesia during surgery in small animal veterinary medicine are discussed below.

1.3.1 Opioids

Opioids are a drug class frequently used in small animals for analgesia. Opioid receptors are found in both peripheral and central nociceptive pathways. There are several types of opioid receptors that have been reported. Antinociceptive effects involve, mu-opioid (μ), kappa-opioid (κ) and delta-opioid (δ) receptors. μ-opioid receptors are responsible for modulating mechanical, chemical, and thermal nociception in nerve endings, joints, spinal cord, and supraspinal areas. Potential complications result from binding to μ-opioid are respiratory depression, miosis, dysphoria and reduced gastrointestinal motility. κ-opioids receptors provide analgesic effects in the spinal cord, but they also cause sedation, miosis, inhibition of ADH release, and dysphoria. δ-opioid receptors provide analgesic and antidepressant effects (Fox 2014b). Once opioids bind to their specific receptors, the conformation of the receptors change, which allows the

association of $G_{i/o}$ proteins with the C terminus. At the location of $G_{i/o}$ proteins, GDP is replaced with GTP at the G_{α} subunit, causing G_{α} and $G_{\beta\gamma}$ to dissociate. The $G_{\beta\gamma}$ subunit inhibits adenylyl cyclase and reduces cyclic adenosine monophosphate (cAMP) production, which is associated with K^+ and Ca^{2+} ion channel activity. After opioids bind to receptors, the K^+ ion channels in the postsynaptic membrane open, thus facilitating hyperpolarization and preventing excitation and propagation of action potentials in the nociceptive pathway. Opioid receptors also act on Ca^{2+} channels by preventing Ca^+ influx, which prevents the excitation and propagation of action potentials and prevents compounds such as SP or CGRP from being released (Stein et al. 2009).

Opioid receptors are found in almost every part of the physiological pain pathway, including in transduction, transmission, modulation, and perception areas. Opioid receptors reside in the terminus of nociceptors and peripheral sensory nerve fibers. These receptors prevent nociceptive impulses by inhibiting Ca^{2+} currents via $G_{i/o}$ proteins, and they also modulate TTX-R Na^+, which generates action potentials in the nociceptive pathway (Stein 1995; Stein et al. 2009).

In the spinal cord, μ- and κ-opioid receptors are present in high concentrations, and κ-receptors are predominant. Opioid receptors are concentrated in the substantia gelatinosa and dorsal horn, where nociceptive fibers synapse. There are several areas in which opioid receptors are found; μ-receptors are found predominantly in the brainstem and neocortex, and κ-receptors are concentrated in the hypothalamus, periaqueductal gray, substantia nigra, and deep laminae of the neocortex. The crucial areas that respond to the antinociceptive effect are the periaqueductal gray and the floor of the fourth ventricle (Murkin 1991). Opioid receptors are found in almost every part of the physiological pain pathway, allowing opioids to affect multiple sites for antinociception. Opioid drugs have different affinities for the different receptors, and the final effect can be different. Below, details of the commonly used opioid drugs are discussed.

Morphine has a high affinity for μ opioid receptors and affinity for κ-receptors. The drug is commonly used for perioperative pain management due to its analgesic efficacy, safety, and cost-effectiveness. The analgesic effect can last approximately 2-4 hours. However, complications often observed in dogs are nausea, vomiting, sedation, panting, bradycardia, respiratory depression, and

dysphoria. Histamine can be released if given intravenously, and it results in hypotension. (Pascoe 2000; Fox 2014b; Kukanich & Wiese 2015).

Hydromorphone, also a full μ-opioid agonist with similar analgesic effects to morphine but 5-7 times greater potency. Hydromorphone is less likely to produce histamine release when administered intravenously. The analgesic effect lasts approximately 2-6 hours. It provides a good level of sedation, which is why it is commonly used for anesthesia premedication in veterinary medicine (Pascoe 2000; Fox 2014b; Kukanich & Wiese 2015).

Fentanyl is one of the most common opioids used for severe pain in small animal medicine, especially dogs. It has a short duration and rapid onset to allow for better titration and is often used in continuous rate infusion. It is a full μ-opioid agonist 80-150 times more potent than morphine. Fentanyl is also available in a transdermal fentanyl solution form, providing effective analgesia for postoperative patients. The onset of action in dogs is approximately 24 hours with an effect duration up to 72 hours. However, a high variability of effect is observed in dogs, resulting in a higher risk of side effects and lower consistency of adequate analgesia (Pascoe 2000; Fox 2014b; Kukanich & Wiese 2015).

Methadone is a μ-opioids agonist. It has a potency approximately 1-1.5 greater than morphine. Methadone binds to NMDA receptors as an antagonist. The analgesic effect is appropriate for moderate pain and lasts for 4 hours in dogs and greater than 2 hours in cats. Intravenous administration is less likely to cause histamine release. Common complications of other opioids, such as nausea and vomiting, are less likely to be observed when methadone is administered (Pascoe 2000; Ferreira et al. 2011; Fox 2014b; Kukanich & Wiese 2015).

Opioids are commonly used drugs for controlling perioperative pain due to the potent analgesic effects. On the other hand, side effects to consider when using opioid drugs include: cardiovascular depression with bradycardia, gastrointestinal disturbances, behavioral alterations with dysphoria and sedation, respiratory depression, anaphylactic reactions, hypotension from histamine release, and urinary retention. (Pascoe 2000; Nishimori et al. 2006; Fox 2014b; Kukanich & Wiese 2015).

1.3.2 Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a drug class that provides analgesia and anti-inflammatory properties. NSAIDs attenuate the function of cyclooxygenase or prostanoid synthesis enzyme (COX). COX is essential for metabolizing arachidonic acid into prostanoid substances. There are three major types of COX: COX-1 synthesizes thromboxane A_2 (TXA_2) and prostaglandin F (PGF). COX-2 synthesizes prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2). COX-3 is a splice variant of COX-1. It resides mainly in central nervous system and provides analgesia effect from acetaminophen and metamizol. (Muñoz et al. 2010; KuKanich et al. 2012). Prostaglandins are crucial mediators for developing inflammation by peripheral and central sensitization. The inhibition of COX in the periphery and dorsal horn provides anti-inflammatory and analgesic effects. NSAIDs provide good analgesia results when given concomitant with other analgesic drugs, such as opioids. Common adverse effects observed with NSAIDs are gastrointestinal disorders with gastric irritation and ulcers, renal injuries, and coagulopathies. The decrease in prostaglandin synthesis can decrease blood flow to the gastric mucosa with decreased mucoprotective and bicarbonate secretions. This effect predisposes to gastric ulcerations. In the kidney, the decline in prostaglandin concentrations can decrease renal blood flow, reduce glomerular filtration rate, and predispose to nephrotoxicity. Inhibition of COX may decrease thromboxane A_2 production, which interferes with platelet aggregation. NSAID anti-inflammatory and analgesic properties are not potent enough for severe pain. For this reason, NSAIDs are often used in combination with other analgesic drugs for adequate perioperative analgesia (balanced anesthesia and analgesia). The perioperative analgesic effects from these combinations can be superior to the additive effect of each drug individually (Fowler et al. 2003; Lemke & Creighton 2010; Borer-Weir 2014; Papich & Messenger 2015).

1.3.3 Alpha-2 agonists (α-2 agonist)

Alpha-2 agonists are drugs commonly used in veterinary medicine. Following its group name, this group of drugs act mainly but are not limited by binding to α-2 receptors. In the central nervous system, the binding of α-2 adrenergic receptors leads to sedation, analgesia, muscle relaxation, mediates heart rate and afterload by decreasing sympathetic function. The sedation effects have been associated with receptors

located in the pons area (locus coeruleus) and rostroventral lateral medulla. This effect may also involve changes to sympathetic outflow modulations. In addition, α-2 drugs bind to receptors in the dorsal horn of the spinal cord, causing additional analgesia. The side effects observed when using α-2 drugs are cardiovascular complications that consist of a two-phase response. The first phase results from the activation of post-synaptic α-2 receptors in vascular smooth muscle, which increases peripheral vasoconstriction and causes blood pressure to rise. This effect involves vagal tone and decreases heart rate. The second phase involves an hypotension effect, which is associated with decreased sympathetic tone. During this phase, blood pressure is reduced along with a prolonged decrease in heart rate. Decreased cardiac output is the result. Moreover, the drug can cause cardiac arrhythmia such as first and second atrioventricular heart block. If an anticholinergic drug is administered concurrently, ventricular arrhythmia and ventricular bigeminy can also be found (Murrell & Hellebrekers 2005; Congdon et al. 2011). Respiratory depression occurs secondary to depression of the central nervous system associated with α-2 adrenergic stimulation. The degree of depression is significant, especially when given in combination with other drugs, such as opioids. Respiratory depression results in a decreased respiratory rate, increased arterial tidal carbon dioxide tension, hypoxemia, or even cyanosis (Sinclair 2003). The α-2 agonist can suppress insulin release and stimulate glucagon release that can induce hyperglycemia. Therefore, the drug should not be used in patients undergoing a glucose tolerance test (Sinclair 2003; Clark et al. 2014). The α-2 agonist also inhibits antidiuretic hormone, which affects the renal tubules and causes a large volume of urine production with low specificity. Thus, it should not use of the drug in the patient with a urinary tract obstruction (Sinclair 2003). The α-2 agonist commonly used in small animals is dexmedetomidine. This drug is used as a sedative for minor procedures, as premedication for anesthesia, and postoperatively for resolving dysphoria/emergence delirium. Drugs in this group provide multifunctional effects, benefiting patients who have undergone surgery and minor procedures. However, the cardiovascular and respiratory complications may limit its use. Therefore, the drug is most suitable for healthy patients (Lemke & Creighton 2010; Congdon et al. 2011; Rankin 2015).

1.3.4 Ketamine

Ketamine is an anesthesia agent that dissociates the thalamocortical and limbic systems and results in loss of awareness. However, ketamine is not only an anesthetic agent; it also modifies nociceptive impulses and alleviates perioperative pain. Ketamine provides analgesia by minimizing central sensitization. The drug decreases central sensitization activity by blocking NMDA receptors and preventing the wind-up mechanism in the dorsal horn. Ketamine acts as an analgesic adjuvant and provides good postoperative analgesia. Side effects often observed with ketamine used include muscle fasciculations (Franco et al. 2018), dysphoria, salivation, tachycardia, increased intraocular pressure and intracranial pressure. (Wagner et al. 2002; Boscan et al. 2005; Sarrau et al. 2007; Berry 2015). Ketamine is often used in combination with multimodal analgesic management.

1.3.5 Gabapentin and pregabalin

Gabapentin was initially used as an additional drug for anticonvulsant purposes based on studies in humans (Zaccara et al. 2021). Studies in dogs have not shown efficacy in controlling seizures, however, complications were found, including sedation and hindlimb ataxia. The cost of the drug also limits its use in large dogs. Therefore, gabapentin is not recommended to control seizures in dogs (Govendir et al. 2005; Platt et al. 2006; Bhatti et al. 2015; Podell et al. 2016). Nevertheless, the drug has shown to be beneficial for treating pain in dogs. The mechanism of action is considered to be at the α-2-δ subunit of presynaptic calcium channels, resulting in the inhibition of calcium influx and prevention of excitatory neurotransmitter release. The mechanism primarily resides in the dorsal horn. The effect reduces neurotransmitter release such as substance P and glutamate, which decrease nociceptive impulses (Crociolli et al. 2015). Moreover, gabapentin can block sodium channels eliminating ectopic impulses and preventing neuropathic pain development (Guy et al. 2014). Two studies in dogs using gabapentin to prevent postoperative pain after mastectomy and intervertebral disc herniation surgery showed lower requirements for rescue analgesia. However, gabapentin does not provide adequate postoperative analgesia by itself, so it is used as an adjuvant for balanced analgesia (Wagner et al. 2010; Aghighi et al. 2012; Crociolli et al. 2015). Pregabalin is a drug that has a structure similar to gabapentin, but it has better bioavailability and a longer half-life (Salazar et

al. 2009). Research on the use of pregabalin for perioperative treatment is very limited; there is only one study of its use in intervertebral disc herniation surgery (Schmierer et al. 2020). In humans, pregabalin showed a better postoperative analgesic effect than gabapentin (Eidy et al. 2017). Further investigation of pregabalin use in veterinary medicine is needed. When weighing the use of pregabalin over gabapentin cost of the drug (which is more expensive than gabapentin) must be considered.

1.3.6 Local anesthesia

Drugs with local anesthetic properties are those that provide anesthesia either locally or regionally. The local anesthesia effect is mediated by inhibiting voltage-gated sodium channels and nerve conduction properties. Once the local anesthetic binds, depolarization of the cell membrane is interrupted, and the nerve impulse ceases. Propagation of the action potential is prevented, and nociceptive pain transmission is stopped. Local anesthetic drugs consist of three main components: a lipophilic aromatic ring, intermediate linkage, and a tertiary amine. This compound gives the molecule both lipophilic and hydrophilic properties. The lipophilic aromatic ring facilitates the drug to cross the neuronal membrane. The intermediate chain allows the local anesthetic to be classified into amino amide and amino ester groups. This intermediate chain determines the elimination pattern of the drug. The amino amide local anesthetic group is biotransformed in the liver, and the drug in the amino ester group is hydrolyzed by plasma esterase in the bloodstream. The tertiary amine has a lipid-soluble property, but once the structure is transformed into a quaternary form, it provides a positive charge to the molecule. This positive charge generates the hydrophilic property of the local anesthetic drug. This hydrophilic property determines the level of water solubility for local anesthetics, allowing the molecule to dissociate from or combine with Na^+ channels.

The pharmacological effects of local anesthetics are influenced by the chemical structure. Lipid solubility, protein binding, and pKa determine local anesthetics' potency, onset, and elimination. Lipid solubility promotes a molecule to penetrate the neural membrane, which accelerates the potency of the drug. Local anesthetic molecules with high lipid solubility may diffuse better in myelin and other lipid-soluble compartments. The local anesthetic molecule is slowly released from the lipid compartment, which causes delayed onset and prolongs the duration of action. The protein-binding properties of local anesthetics impact

the capacity to bind to α_1-acid glycoprotein or albumin in plasma. Only unbound drug molecules have clinical effects. Drugs bound to proteins have a lower capability of elimination. Another important drug property is pKa, which determines at what pH the drug is equally unionized and in ionized form. The unionized form is lipid-soluble, allowing the molecule to pass through the cell membrane. Once the drug passes into a cell, the ionized form binds to Na^+ channels to elicit a clinical effect. Generally, local anesthetic drugs are weak bases with pKa between eight and nine. If the environmental pH is low, such as during inflammation, the local anesthetic tends to be in an ionized form, decreasing its capacity to pass through the cell membrane, and the drug may not effectively provide an analgesic effect.

Local anesthetic drugs are classified into two groups by intermediate linkage, amino esters, and amino amides. The amino ester group consists of procaine, chloroprocaine, and tetracaine, which have lower potency, short onset, short duration, and low capacity to infiltrate tissue. The amino amide local anesthetics frequently used include lidocaine, bupivacaine, levobupivacaine, and ropivacaine (Ruetsch et al. 2001; Martin-Flores 2013; Garcia 2015).

Lidocaine has a short onset of action (10-15 minutes), with a duration of approximately 60 to 120 minutes. The duration of analgesia can be extended to 180 minutes when used in combination with epinephrine. Epinephrine action is associated with the blood flow to the injection site. Blood flow at the site of injection influences the duration that the drug will stay in the target area. The greater the blood flow, the greater the absorption of the local anesthetic from the injection sites. This allows the use of epinephrine as a combination with a local anesthetic to create vasoconstriction to reduce drug uptake. As a result, the decreased local anesthetic uptake can extend the duration of the blockade (Martin-Flores 2013).

Lidocaine comes in various formulations, including solutions for injection, sprays, and patches. In addition to its local analgesic effects, intravenous lidocaine also has benefits to treat cardiac arrhythmia, offer systemic analgesic and minimum alveolar concentration (MAC) reduction (Woolf & Wall 1986; Lemke & Dawson 2000; Martin-Flores 2013; Garcia 2015). It is not recommended to use lidocaine above 12 mg/kg in dogs for local anesthetic purposes (Lemke & Dawson 2000). A toxic dose can cause muscle tremor at 11.1 mg/kg. Seizure can result with an intravenous dose of 20 mg/kg (Feldman et al. 1989; Lemo

et al. 2007). Lidocaine can cause central nervous system toxicity that manifests with convulsions, seizures, coma, and even death. The drug causes neurotoxicity by inhibiting inhibitory cortical neurons in the temporal lobe or the amygdala, causing neurons to become excited, which leads to a range of adverse activities, from muscle twitching to grand mal seizures. If the plasma concentration increases, depression, unconsciousness and coma may be observed (Garcia 2015). Moreover, lidocaine is the only drug in the local analgesia group that can be used intravenously to relieve pain (Grubb et al. 2020).

Bupivacaine has a butyl group on the piperidine nitrogen atom of the molecule. It is a long-acting local anesthetic that lasts for 2-5 hours when given epidurally and 4-12 hours when given to stop nerve conduction, but the onset of action is slow. The downside of bupivacaine is its cardiotoxicity, which is greater than that of other local anesthetics (Morrison et al. 2000). Cardiotoxicity from local anesthetics manifests in arrhythmia, including ventricular tachycardia, ventricular fibrillation, and possible cardiovascular collapse and death (Gristwood 2002). Central nervous system adverse effects leading to death have also been reported following intravascular injection (Feldman et al. 1989).

Levobupivacaine is the bupivacaine "*S"* enantiomer. In human medicine, levobupivacaine is used for its reduced cardiovascular complications, particularly its negative inotropic effect compared with bupivacaine (Bardsley et al. 1998; Nau et al. 2000). In dogs, the cardiotoxicity effect is not different between levobupivacaine and bupivacaine (Groban et al. 2000). Levobupivacaine and bupivacaine are used interchangeably owing to their equipotent properties without differences in the occurrence of adverse effects found in an intrathecal study (Sarotti et al. 2011).

Liposomal bupivacaine is designed to extend the duration of action. Encapsulated liposomes slowly break down to release bupivacaine over 96 hours. These liposomes have shown a higher safety profile than bupivacaine when administered through intravascular, epidural, and intrathecal routes (Joshi et al. 2015). The effects of postoperative analgesia have been revealed in dogs undergoing surgery to correct cranial cruciate ligament insufficiency. The analgesic effect lasted for 72 hours. (Lascelles et al. 2016).

Ropivacaine is an amino amide local anesthetic with a propyl group on the piperidine nitrogen atom of the molecule with a single "*S"* enantiomer. Ropivacaine does not cause localized irritation in the

peripheral nerve or spinal cord. The onsets of action of ropivacaine and bupivacaine are similar due to their similar pKa values of 8 and 8.1, respectively. The duration of action of ropivacaine is shorter than that of bupivacaine owing to lipid solubility, protein binding, and vasodilation activities (Feldman et al. 1996). The onset of ropivacaine is 5 to 10 minutes, and the duration of action is 180-300 minutes (Feldman & Covino 1988). Ropivacaine can be considered superior to bupivacaine due to its lower cardiotoxicity (Feldman et al. 1989; Groban et al. 2001; Schwoerer et al. 2015).

Pain is a major concern in veterinary practice. The deleterious consequences of pain have brought about the development of safer and more effective pain management strategies. Perioperative and multimodal analgesia techniques are used for alleviating pain. Several drugs can be used concomitantly for better analgesia results. The drugs can be administered systemically or locally (Hug et al. 1981; Lucas et al. 2001; Klinge & Sawyer 2013; Tan et al. 2015). Systemic analgesia can provide a satisfactory analgesic effect if given a high dose, leading to side effects (Kona-Boun et al. 2006). The use of local anesthetics as a part of multimodal analgesia is intended to provide adequate analgesia with fewer complications (Romano et al. 2016). Therefore, a loco-regional anesthesia technique can be an important part of the pain alleviation strategy in animals.

For my PhD candidacy and dissertation, we developed a regional analgesia technique using local anesthesia drugs to better manage perioperative orthopedic surgery pain in dogs. My study goals were to develop a safe and practical protocol to improve the analgesia effect for stifle surgery in dogs.

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CHAPTER 2: CRANIAL CRUCIATE LIGAMENT DISEASE

Cranial cruciate ligament (CCL) disease is a common orthopedic disorder in dogs (Johnson et al. 1989). The condition renders the stifle joint unstable and leads to the development of degenerative joint disease. The disease causes significant pain, limb dysfunction and decreases quality of life. Subsequently, surgical treatment has been developed to promote stabilization of the stifle joint (Johnson et al. 1989; Innes et al. 2000; Cook 2010; Comerford et al. 2011). As the number of dogs with CCL disease per year reported in the USA was approximately 270,869 in 2003, the economic impact on veterinary economics and veterinary clients is significant (Wilke et al. 2005; Nicoll et al. 2014). Between 2008 and 2013, the average dog owner's cost to treat CCL disease for their dog was CAD$3,480-3,500 in Canada (Nicoll et al. 2014). My Ph.D. research and dissertation consist of developing and improving a regional analgesia technique to i) improve anesthesia quality and safety, ii) provide better surgical analgesia, iii) provide better postoperative analgesia, iv) ensure better recovery quality, and v) minimize the financial impact of veterinary care.

In this chapter, I discuss and explain the essential anatomy and surgical treatment approaches for CCL disease in dogs, for which I will develop and improve a regional analgesia technique.

2.1. Anatomy

The CCL is a ligament located within the stifle joint. The stifle joint is a complex condylar synovial joint. It integrates the distal femur, proximal tibia, proximal fibula, patella, fabellae, popliteal sesamoid bone, joint capsule, ligaments, menisci, and pelvic limb muscles, which are all essential for stifle joint motion and stability. The primary movements of the stifle joint are tibial and fibular flexion and extension (Carpenter & Cooper 2000; Kowaleski et al. 2012). Four ligaments are integral for joint stability: the CCL, the caudal cruciate ligament, and the medial and lateral collateral ligaments (Evans 1993; Carpenter & Cooper 2000; Hermanson 2013). Each ligament functions to stabilize joint motion. The CCL prevents cranial displacement of the tibia, limits the internal rotation of the tibia relative to the femur while the stifle joint is flexed, and prevents hyperextension of the stifle joint (Dupuis & Harari 1993; Harari 1993;

Kowaleski et al. 2012). It originates at the caudomedial aspect of the lateral femoral condyle, runs spirally, and inserts into the cranial intercondylar area of the tibia (Carpenter & Cooper 2000) (Figure 2.1). Another ligament that runs in the opposite direction to the CCL is the caudal cruciate ligament, which originates on the lateral side of the medial femoral condyle and inserts at the popliteal notch of the tibia. The function of the caudal cruciate ligament is to prevent caudal displacement (Carpenter & Cooper 2000). Blood flow to both cruciate ligaments is supplied by the medial and lateral genicular arteries via the synovial membrane covering the ligaments. However, blood flow is not supplied evenly to both ligaments. Fewer vessels supply the CCL than the caudal cruciate ligament, which reduces its ability to recover from injury. As a result, diseases associated with the CCL are more common than diseases associated with the caudal cruciate ligament (Hermanson 2013). The other two ligaments supporting the stifle joint, the medial and lateral collateral ligaments, stabilize the joint during flexion and extension. During extension, both collateral ligaments act together with the CCL to prevent internal rotation of the tibia. While the stifle joint is flexed, the lateral collateral ligament is less taut, allowing the cruciate to play a major role in limiting internal rotation of the tibia. Lateral rotation is restrained by the collateral ligaments in both extension and flexion. These ligaments work concordantly to create the appropriate movement of the stifle joint (Evans 1993; Hermanson 2013).

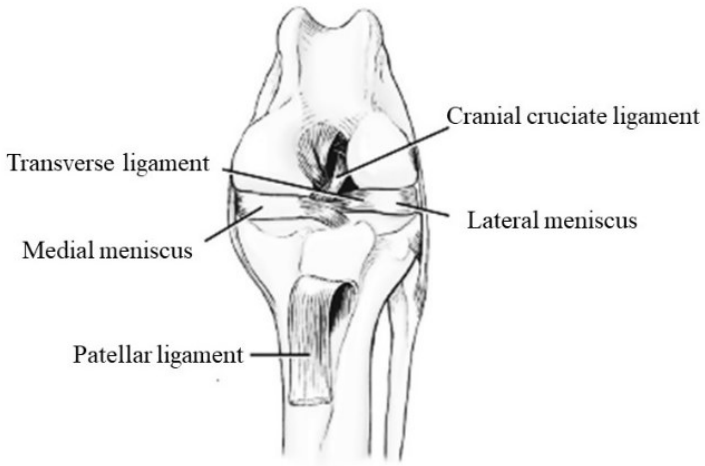

Figure 2.1 Cranial view of the flexed right stifle joint. In the figure, the proximal part of the patellar ligament has been removed to reveal the structure of the stifle joint (adapted from Evans (1993)

The stifle joint is vastly innervated by nerves that are crucial for facilitating the movement and sensation of the joint. The innervation of the stifle joint is formed by the medial articular nerve, posterior articular nerve, and lateral articular nerve. The medial articular nerve is a branch of the saphenous nerve, with supplemental fibers from the femoral nerve and obturator nerve. The medial articular nerve runs to the stifle joint along the adductor magnus, adductor brevis, and vastus medialis. The medial articular nerve is divided into several branches to supply its destination at the level where the medial collateral ligament attaches to the femur. The medial articular nerve innervates the medial collateral ligament and the medial, anteromedial, and posteromedial aspects of the joint capsule tissue. Some of the branches innervate the capsule proper, infrapatellar fat pad, CCL, caudal cruciate ligament, and posterior horn of the lateral meniscus. The posterior articular nerve is a branch of the tibial nerve. This tibial-derived nerve innervates the posterior area of the stifle joint. The lateral articular nerve is a branch of the common peroneal nerve. Proximal to the neck of the fibula, the nerve arises as one branch or is separated into several branches to supply the superior tibiofibular joint, lateral collateral ligament, and lateral and posterolateral aspects of the joint capsule (Figures 2.2 and 2.3) (O'Connor & Woodbury 1982; Evans 1993).

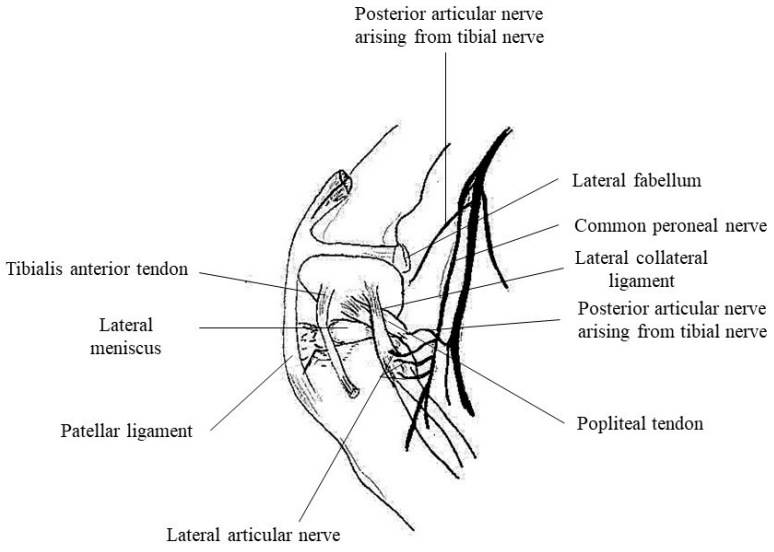

Figure 2.2 Medial view of a dog's stifle joint innervation (adapted from O'Connor and Woodbury (1982)).

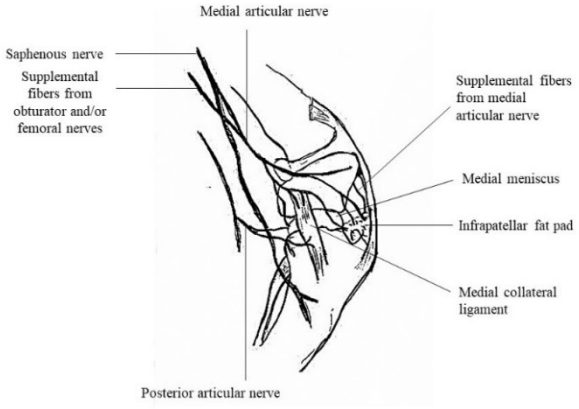

Figure 2.3 Lateral view of a dog's stifle joint innervation (adapted from O'Connor and Woodbury (1982)).

The soft tissue structures associated with the stifle joint (muscle and skin) are innervated by nerves derived from the lumbar plexus and sciatic nerve. The lumbar plexus consists of intercommunication among ventral branches of the third, fourth, and fifth lumbar nerves. Some fine branches from the second and sixth lumbar nerves may also interconnect to form the plexus. The lumbar plexus is located within the psoas compartment. The psoas compartment consists of the psoas major, psoas minor, and quadratus lumborum muscles. After the regional nerves join the lumbar plexus, each nerve travels caudally and leaves the compartment to innervate its target area (Kitchell 2013; Portela et al. 2013). The lumbar plexus is the precursor for the following nerves that innervate the stifle area: the lateral femoral cutaneous, genitofemoral, femoral, saphenous, and obturator nerves (Figure 2.4). These are nerves to consider when developing an analgesia plan for the stifle area.

The lateral femoral cutaneous nerve is formed primarily by ventral branches of the fourth lumbar nerve. Some interconnections from the third and fifth lumbar nerves may be found. The lateral femoral cutaneous nerve runs caudolaterally through the psoas minor muscle. The nerve travels to the abdominal wall through the internal and external abdominal oblique muscles. The nerve innervates three major cutaneous areas: the surface from the tuber coxae region to the cranial part of the pelvic region, the cranial portion of the thigh, and the lateral area of the stifle joint (Evans 1993).

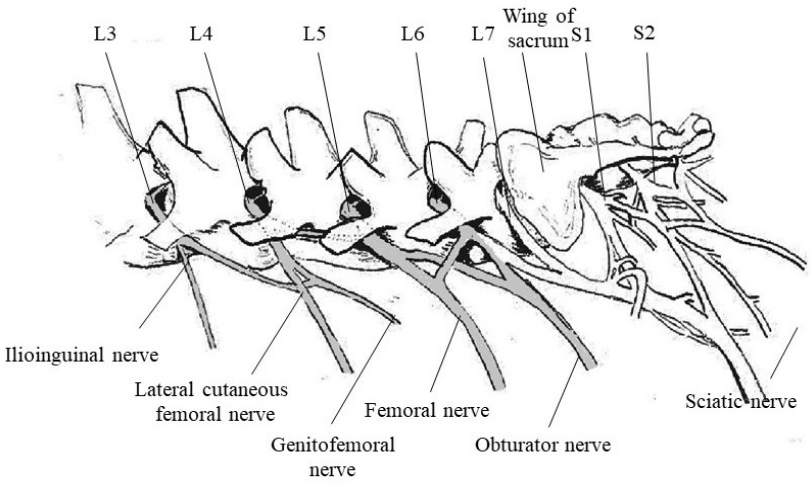

Figure 2.4 Lateral view of the spine, lumbar nerves, sacral nerves, and nerve formation. L3, 3rd lumbar nerve; L4, 4th lumbar nerve; L5, 5th lumbar nerve; L6, 6th lumbar nerve; L7, 7th lumbar nerve; S1, 1st sacral nerve; S2, 2nd sacral nerve. The lumbar plexus consists of a ventral branch from the 3rd to 6th lumbar nerves. In some dogs, nerves from the ventral branch of the 2nd and 6th lumbar nerves may interconnect to form the plexus (grey color nerves). The sciatic nerve consists of the ventral branch from ventral branch of the 6th to 7th lumbar nerves and 1st sacral nerve. In some dogs, the ventral branch of the 2nd sacral nerve is interconnected to form the sciatic nerve (white color nerves). (adapted from Kitchell (2013)).

The genitofemoral nerve is formed by the ventral nerve roots of the third and fourth lumbar nerves. The genitofemoral nerve enters the psoas compartment near the fourth lumbar vertebral area. The nerve has two major branches: the genital and femoral branches. The genital branch supplies the skin around the pudendal region. The femoral branch runs caudolaterally and distally to supply the skin on the proximomedial area of the thigh (Kitchell 2013).

The majority of the femoral nerve arises from the fifth lumbar nerve. However, nerve fibers from the fourth and sixth lumbar roots have been reported. The nerve enters the psoas minor muscle and travels along the caudal portion of the psoas major muscle. Shortly after the femoral nerve enters the quadriceps femoris, the femoral nerve reaches the quadriceps muscle and supplies all four heads of the quadriceps muscle and articular coxae. Nerve branches derived from the femoral nerve are mostly motor nerves, with very few sensory nerves.

The saphenous nerve resides in the superficial area of the femoral nerve. It branches from the femoral nerve before leaving the psoas major muscle. The nerve runs along the medial surface of the tensor fascia lata and divides into muscular and cutaneous branches. The muscular branch innervates the sartorius

muscle, while the cutaneous branch lies cranially to the femoral artery and runs distally. The cutaneous branch innervates the skin of the middle and distal medial surfaces of the thigh. Proximal to the stifle joint, the cutaneous branch runs to the medial surface of the stifle joint, forming the medial articular nerve that innervates the medial collateral ligament and capsular tissue. Distal to the stifle joint, this branch of the saphenous nerve supplies the skin surrounding the tibia, fibula, and paw. This branch is mainly considered a major sensory nerve derived from the femoral nerve (O'Connor & Woodbury 1982; Evans 1993).

The obturator nerve originates from the fourth, fifth, and sixth lumbar nerve roots, with a significant contribution from the fifth lumbar nerve. The obturator nerve forms at the caudomedial portion of the psoas major muscle. The nerve exits the psoas major dorsomedially, runs laterally by the shaft of the ilium and exits the pelvis through the obturator foramen. After the nerve exits the pelvis, it branches and supplies the external obturator, pectineus, gracilis, and adductor muscles. In some dogs, a branch from the obturator nerve joins the saphenous nerve and forms part of the medial articular nerve (O'Connor & Woodbury 1982; Evans 1993).

As described, all nerves originating from the lumbar plexus (the lateral femoral cutaneous, genitofemoral, femoral, saphenous, and obturator nerves) play an important role in innervating the stifle joint area. As I developed a regional analgesia technique for stifle surgery, I considered the lumbar plexus and all its nerve branches.

Another nerve that innervates soft tissue structures associated with the stifle joint is the sciatic nerve. The sciatic nerve arises from the sixth and seventh lumbar, the first sacral, and, occasionally, the second sacral nerve roots. After the nerve enters the thigh, it lies over the gemelli muscle and the tendon of the internal obturator muscle caudal to the coxofemoral joint. The nerve travels between the greater trochanter of the femur and ischial tuberosity. The sciatic nerve runs distally between the bicep femoris, adductor, semitendinosus, and semimembranosus muscles (Mahler & Adogwa 2008). The sciatic nerve gradually divides into the common peroneal and tibial nerves in the proximal two-thirds of the thigh. After the bifurcation, the common peroneal nerve runs deep under the bicep femoris muscle and across the lateral head of the gastrocnemius muscle. The common peroneal nerve forms the lateral articular nerve to supply

the lateral collateral ligament and lateral aspect of the stifle joint. The common peroneal nerve continues to travel distally and separates into superficial and deep fibular nerves around the area near the lateral head of the gastrocnemius. The superficial fibular nerve innervates the fibularis brevis, lateral digital extensor, digits, and skin of the craniolateral aspect of the crus and tarsus. The deep fibular nerve supplies the fibularis longus, long digital extensor muscle, tibialis cranialis, and skin of the dorsal interdigital area between digits II and III. The other branch from the sciatic nerve, the tibial nerve, innervates the caudal aspect of the stifle joint and forms the posterior articular nerve (O'Connor & Woodbury 1982; Evans 1993). The tibial nerve continues distally, innervating the caudal aspect of the tibia and fibula and the tarsal and digital joints.

The lumbar plexus and sciatic nerve provide most of the innervation involved in stifle joint sensory information and pain sensation. To develop and improve pain management of the stifle joint and surrounding area, familiarity with the innervation is important.

2.2 Cranial cruciate ligament disease

CCL disease causes severe joint instability, leading to further osteoarthritis with significant pain and dysfunction (Cook 2010). The disease has a multifactorial etiology; it can occur from acute trauma, ligament disease, or postural abnormalities (Vasseur et al. 1985; Hayashi et al. 2004; Comerford et al. 2011). The predisposing factors for CCL disease include breed, body weight, and age. The breeds prone to CCL disease include Rottweiler, Newfoundland, Labrador retriever, Golden retriever, West Highland white terrier, Yorkshire terrier, and Staffordshire bull terrier (Whitehair et al. 1993; Wilke et al. 2006; Taylor-Brown et al. 2015). Breed may play a role due to the phenotype of the ligament. For example, one study showed that the CCL in Rottweilers required less force to be torn when compared with the racing Greyhound. This indicates that the CCL in Rottweilers is vulnerable to tearing, which may be associated with inherent ligament collagen defects of the breed (Wingfield et al. 2000). Overweight dogs can develop CCL disease due to the increased ligament stress from the greater load (Taylor-Brown et al. 2015). Dogs aged 9-10 years have 5.5 greater odds of developing CCL disease than younger dogs (less than three years), which may be associated with ligament degeneration (Taylor-Brown et al. 2015). Therefore, breed, body weight, and age are predisposing conditions for the development of CCL disease.

When the CCL is damaged or ruptured, the joint function and structure are altered (Korvick et al. 1994b). In normal dogs, the CCL is important in resisting the force translated to the tibia cranially relative to the femur and resisting tibial internal rotation during flexion. Once the CCL ruptures, the tibia moves cranially with regard to the femur, and excessive internal rotation of the tibia occurs when the joint is flexed. This joint instability may cause degeneration of the articular cartilage and inflammation, predisposing it to periarticular osteophytes and damage to the meniscus (Johnson & Johnson 1993). As a result, dogs that develop pain associated with CCL disease show signs of lameness, are partial to non-weight-bearing activities and have difficulty standing and sitting (Schulz 2013).

2.2.1 CCL disease diagnosis

Diagnosing CCL disease requires canine patient signalment, clinical signs, and orthopedic and radiographic examinations (DeCamp et al. 2016). Clinical signs are crucial for diagnosis. The disease progresses in different phases. In the early phase of the disease, dogs are non-weight-bearing or lame, which usually improves within 3-6 weeks (Schulz 2013). This ameliorating clinical sign may last for months and suddenly deteriorate, often from meniscal damage. During this period, osteoarthritis progresses with declining stifle joint function (DeCamp et al. 2016).

Physical examination is crucial for diagnosing CCL disease. The disease may lead the patient to postural and conformational abnormalities and lameness. Abnormalities such as straight stifle and hock, atrophy of the quadriceps muscle, and thickness of the joint capsule on the medial aspect can be found in patients with CCL disease. Moreover, drawer tests and tibial compression thrust tests are used to help clinicians diagnose the disease. The drawer test is performed when the dog is in lateral recumbency with the test leg placed in an uppermost position. The first hand holds the distal part of the femur, the thumb is placed caudal to the lateral fabella, and the index finger is placed on the patella. Another hand holds the tibia by placing the index finger on the tibial crest, and the thumb is placed on the caudal side of the fibular head. The femur is stabilized, and the tibia is pushed forward and pulled backward. The technique is performed several times in flexion and extension. Cranial advancement of the tibia relative to the femur is a positive drawer sign, which indicates CCL disease (Figure 2.5). The tibial compression thrust test is

performed in lateral recumbency with the test limb placed in the uppermost position, and the test is performed in an extended stifle position. The index finger of the first hand is placed on the tibial crest, and the thumb and the middle finger hold the distal end of the femur. The index finger is used to apply pressure in the caudal direction. Another hand holds the metatarsal to flex and extend the hock joint. Once the metatarsal region is dorsiflexed, the gastrocnemius contracts and the tibia is advanced cranially, which can be noticed by the index finger placed on the tibial crest. This cranial advance of the tibial crest indicates CCL rupture (DeCamp et al. 2016) (Figure 2.6). These tests are useful for acute CCL injury. Still, for chronic injury, false-negative results may be present if the periarticular tissue is thickened and fibrotic, which may limit tibial cranial motion.

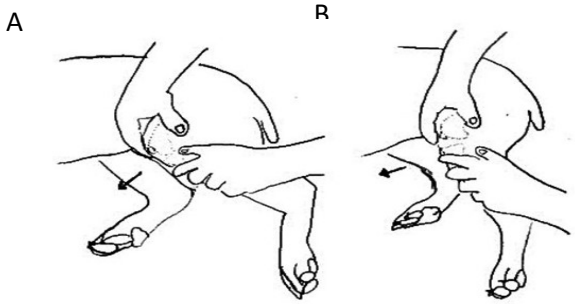

Figure 2.5 Direct drawer test. A) Clinical sign of a dog with a negative drawer sign; the tibia is not advanced cranially relative to the femur. B) Clinical sign of a dog with a positive drawer sign; the tibia is advanced cranially relative to the femur (adapted from DeCamp et al. (2016).

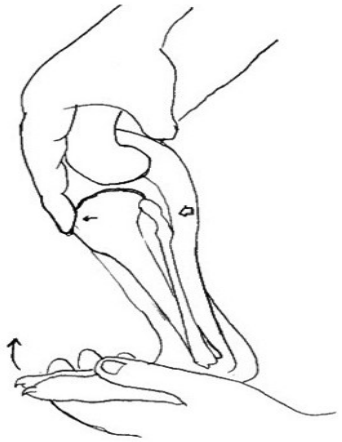

Figure 2.6 Tibial compression thrust test. Depicts the hand and finger positions and the direction of paw flexion (adapted from DeCamp et al. (2016)).

Radiographic imaging is used to diagnose dogs suspected of having subtle or absent drawer motion (Bree et al. 2010). It is also important to assess osteoarthritis and rule out fracture or neoplasia. Radiographs of CCL patients may reveal cranial displacement of the tibia relative to the femur, osteophytes in the stifle joint, fat pad signs due to synovial effusion, or fibrosis deposited in this region, and avulsion fractures (Kealy et al. 2011; DeCamp et al. 2016).

2.2.2 Treatment

When CCL disease has been diagnosed, the progression can be managed or treated either medically or surgically. Medical management aims to improve dog comfort, limb function, and quality of life. The management often involves reducing weight, physical therapy, exercise, rehabilitation, and providing long-term analgesia. The success rate for medical management depends on the ability to lose weight, the use of analgesia drugs, and appropriate physical therapy. It has been reported that medical management success is around 47% (Wucherer et al. 2013).

Surgical management for CCL disease aims to stabilize the stifle joint. A stable joint will reduce and mitigate pain, delay osteoarthritis and provide structural support (DeCamp et al. 2016). Surgical correction can occur via intracapsular ligament replacement, extracapsular suture techniques, and neutralizing dynamic osteotomy techniques (Kowaleski et al. 2012; DeCamp et al. 2016).

The intracapsular stabilization technique is associated with the replacement or reconstruction of the CCL with autogenous or synthetic materials (DeCamp et al. 2016). Autographs from the fascia lata, patellar ligament, or quadriceps tendon have been used to functionally stabilize the joint and mimic the CCL (Korvick et al. 1994a; DeCamp et al. 2016). A different option is using a synthetic graft. The intracapsular stabilization technique improves lameness scores when compared with the preoperative period, but it does not stabilize the stifle joint in the long term (Barnhart et al. 2016). The intracapsular technique does not provide better force plate evaluation results with a longer duration of lameness when compared to other techniques (Molsa et al. 2013; Molsa et al. 2014). In addition, artificial grafts can cause foreign body reactions triggering synovitis and osteoarthritis (Stead et al. 1991; Geels et al. 2000). Consequently, the intraarticular method is not frequently utilized in veterinary medicine (Comerford et al. 2013).

Extracapsular stabilization is a common method to treat CCL disease in small dogs (Duerr et al. 2014). The method uses heavy-gauge sutures to increase joint stability (DeCamp et al. 2016). Lateral fabellotibial sutures are frequently utilized for extracapsular techniques (Bergh et al. 2014). This technique uses heavy, nonabsorbable monofilament nylon that passes through a tunnel drilled at the tibial crest, positioning the sutures around the lateral fabella and securing them with a knot or a tension device (Kowaleski et al. 2012). The extracapsular technique causes immediate postoperative stability, but it eliminates internal rotation of the tibia during stifle flexion. Thus, a limitation is further damage to the articular cartilage and menisci (Jerram & Walker 2003). The technique is usually used to treat CCL disease in dogs under 15 kg (Duerr et al. 2014).

The two most common neutralizing dynamic osteotomy techniques performed in dogs with CCL disease are tibial tuberosity advancement (TTA) and tibial plateau leveling osteotomy (TPLO) (Duerr et al. 2014). The theory behind TTA assumes that the tibiofemoral compressive force is approximately parallel to the patellar ligament and allows the tibiofemoral shear force to change dynamically by the movement of the joint. The tibiofemoral shear force is directed anteriorly when the knee joint is extended, and the force is directed posteriorly when the knee joint is flexed. The technique is accomplished by freeing the tibial tuberosity with an oscillating saw. The tibial tuberosity is advanced cranially, and the patellar ligament is adjusted to make a 90-degree angle with the tibial plateau. A cage is placed proximally between the tibial tuberosity and tibial shaft to retain the gap and keep the angle at the target degree. The tibial tuberosity and tibial shaft are secured by a tension band plate (Lafaver et al. 2007; Boudrieau 2009; DeCamp et al. 2016) (Figure 2.7). The benefit of the TTA technique is that it does not change the joint geometry, and the cartilage pressure distribution is better than that with TPLO for correcting CCL disease. TTA can be used in dogs who already have a small tibial plateau slope, for which TPLO is not a good choice for treatment (Boudrieau 2009). However, TTA has disadvantages, and it is not suitable for dogs with an excessive tibial plateau slope, limb deformities, or patellar luxation (Boudrieau 2009).

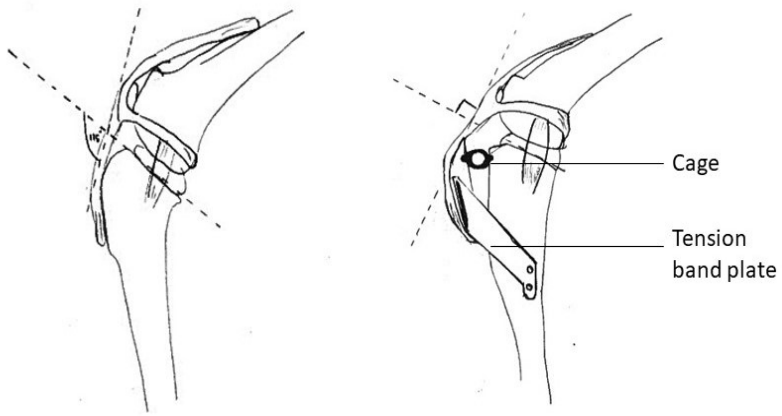

Figure 2.7 Tibial tuberosity advancement. A) The angle between the patellar ligament and tibial plateau is greater than 90 degrees, which allows the tibia to move cranially. B) After correction, the angle between the patellar ligament and the tibial plateau is 90 degrees. A metal cage is placed at the proximal area between the tibial crest and the shaft to retain the distance between the two compartments, and the tension band plate is placed to secure the compartments.

Tibial plateau leveling osteotomy (TPLO) provides alteration of the joint geometry to eliminate cranial tibial thrust. Cranial tibial thrust is an internally generated force that causes the tibia to translate cranially. The cranial movement is limited by the CCL and strong hamstring, preventing the cranial tibial thrust sign (Boudrieau 2009; DeCamp et al. 2016). TPLO aims to reduce the tibial plateau angle (reduce the slope of the angle) to prevent the cranial tibial thrust sign. The surgical procedure starts by cutting the proximal tibia in a curved form with a biradial saw blade. The proximal tibia is rotated to meet the target angle of the tibial plateau, and the new angle is stabilized to the shaft of the tibia with a TPLO bone plate (Figure 2.8). The technique decreases cranial tibial thrust and drawer motion (Jerram & Walker 2003; Boudrieau 2009; DeCamp et al. 2016). TPLO surgical correction provides better treatment results than other surgical treatments. It improves the clinical-functional outcome by helping the dog return to normal walking and trotting (Krotscheck et al. 2016). In a long-term (3-year follow-up) study, radiographic imaging showed that osteoarthritis was less frequent in dogs treated with TPLO than with TTA (Moore et al. 2020). As a result, TPLO is the most common surgical treatment technique used in dogs to treat CCL disease (von Pfeil et al. 2018).

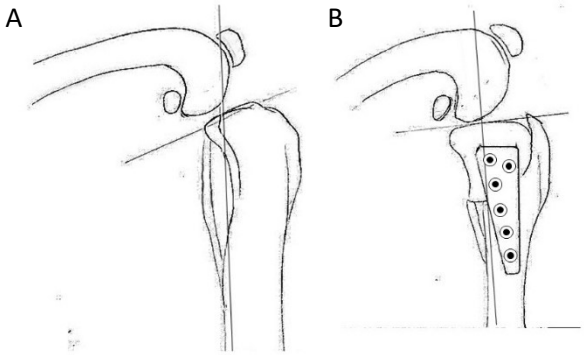

Figure 2.8 Tibial plateau leveling osteotomy. A) Stifle joint before surgical correction. The tibial plateau slope is steep, causing the tibia to translate cranially when the force from the femur reacts with the articular surface of the tibia. B) Stifle joint after surgery. The proximal part of the tibia is cut into a curved form, and the proximal tibia is rotated to decrease the tibial plateau angle. The TPLO bone plate is used to secure the proximal tibia and shaft of the tibia.

Due to the better clinical outcomes and lower complication rates associated with TPLO treatment, the incidence of TPLO surgery is high (Krotscheck et al. 2016; von Pfeil et al. 2018; Moore et al. 2020). It has been documented that 365,400 TPLO surgeries are performed yearly in the USA alone (Wilke et al. 2005; Duerr et al. 2014). For these reasons, my Ph.D. and dissertation are dedicated to improving pain management for TPLO surgery and CCL disease. Adequate pain management is essential for adequate recovery to improve quality of life and return to normal function (Rialland et al. 2012).

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CHAPTER 3: COMMON ANALGESIA TECHNIQUES USED FOR SURGICAL TREATMENT OF CRANIAL CRUCIATE LIGAMENT DISEASE

Surgical treatment for cranial cruciate ligament (CCL) disease is a popular technique for CCL disease (Duerr et al. 2014). Surgical treatment is commonly suggested for patients because of the higher percentage of successful outcomes than nonsurgical treatment (Wucherer et al. 2013; Duerr et al. 2014). However, surgical techniques, especially tibial plateau leveling osteotomy (TPLO), are painful procedures involving soft tissue trauma, arthrotomy, osteotomy, and bone plate application (Vasseur 1984; Hoelzler et al. 2005). Furthermore, surgical treatment for CCL disease causes acute post-operative pain and can predispose to chronic pain. A study reported that approximately 30% of dog owners considered that their dog developed chronic pain after surgical correction for CCL disease (Molsa et al. 2013). Therefore, efficient pain management is essential for dogs undergoing surgical correction for CCL disease. Common analgesia plans for CCL disease surgery can be divided into systemic analgesia and regional analgesia. Systemic analgesia consists of drugs administered systemically, while regional analgesia consists of regional techniques such as intraarticular analgesia, epidural analgesia, or peripheral nerve blocks (Hoelzler et al. 2005; Bufalari et al. 2012; Bartel et al. 2016). In this chapter, I describe the different analgesia options reported for CCL disease surgery in dogs.

3.1 Systemic analgesia

Systemic analgesia has been the predominant form of analgesia and anesthesia since the inception of CCL disease surgery in veterinary medicine. Systemic analgesia is essential for proper anesthesia to facilitate the loss of sensation, immobilization, pain alleviation, amnesia, and muscle relaxation. Preoperatively, systemic analgesia is the easiest and most common approach for pain relief during CCL disease. Postoperatively, systemic analgesia can provide comfort to improve wellbeing from surgical pain (Tranquili & Grimm 2015). The use of multimodal or balance anesthesia to alleviate pain can be achieved by using systemic analgesia. Effective analgesia management is one of the key factors for balanced anesthesia with several benefits for surgery patients. First, it improves anesthetic safety by decreasing other

anesthetic requirements, resulting in reduced complications related to the dose-dependent adverse effects from anesthesia, such as hypotension and hypoventilation. Second, peri-operative analgesia decreases the adverse effects of pain, particularly the behavioral changes that may lead to aggressiveness or severe depression, limit mobility, or reduced appetite (Sharkey 2013). Lastly, peri-operative analgesia can prevent acute pain from progressing to chronic pain (Grubb et al. 2020). Anesthetic drugs such as propofol, alfaxalone, and inhaled anesthetics provide analgesia, but the effect may not be sufficient for major orthopedic surgery without using high doses that potentially can result in side effects (Winter et al. 2003; Trim & Hall 2014; Berry 2015). Systemic analgesic drugs can be administered to decrease the dose of anesthetic drugs, which is the basis of multimodal anesthesia (Lewis et al. 2014; Romano et al. 2016). Common systemic analgesic drugs for balanced anesthesia are opioids, NSAIDs, dexmedetomidine, gabapentin, tramadol, and combinations of morphine, lidocaine, and ketamine (Mathews et al. 2014).

Opioid drugs are often used to manage pain during orthopedic surgery (Pascoe 2000; Chohan 2010). Opioids have potent analgesic effects, especially μ-opioid agonists. Drugs in this group include morphine, hydromorphone, oxymorphone, and methadone, which are frequently used perioperatively for stifle surgery in dogs (Kona-Boun et al. 2006; Moak et al. 2011; Lewis et al. 2014; Soto et al. 2014; Navarrete-Calvo et al. 2016). Lewis et al. (2014) showed that when morphine was used for anesthesia premedication, it offered intraoperative and post-operative analgesia for 24 hours in dogs undergoing TPLO. However, other studies have shown that systemic opioids as the sole mode for analgesia during orthopedic surgery in dogs may require a large dose of opioids or additional analgesia techniques for adequate comfort (Soto et al. 2014; Navarrete-Calvo et al. 2016; Romano et al. 2016). Use of large peri-operative opioid doses for analgesia may trigger side effects such as bradycardia, nausea, vomiting, respiratory depression, urinary retention, dysphoria, delirium, sedation, and poor recovery quality from anesthesia (Nolan & Reid 1991; Valverde et al. 2004; Takahashi et al. 2007; Peterson et al. 2014; Boscan & Wennogle 2016; Romano et al. 2016; Bini et al. 2018). Therefore, opioid side effects should be considered when using this group of drugs systemically.

NSAIDs are a second drug group commonly used systemically as part of balanced anesthesia and analgesia for orthopedic patients. NSAIDs used for stifle surgery in dogs have shown significant benefits (Reese et al. 2000; Fowler et al. 2003; Gruet et al. 2011; Davila et al. 2013). When used perioperatively, the analgesic efficacy and safety are comparable among drugs in the NSAIDs group (Deneuche et al. 2004; Laredo et al. 2004). Meloxicam has been used for post-operative analgesia by giving a subcutaneous injection in dogs receiving CCL surgery. One study showed that the post-operative analgesic effect from meloxicam was not different from the group that did not receive the drug (Moak et al. 2011). Another study showed a synergistic effect of a combination of meloxicam and butorphanol. The drugs were administered in dogs that underwent CCL surgery and showed a slightly better pain scale with lower serum cortisol concentration than the group that received only butorphanol (Budsberg et al. 2002). A study performed by Fowler et al. (2003) showed a better post-operative pain score in dogs who received meloxicam with an epidural block before the surgery. Meloxicam also provided adequate analgesia for 24 hours postoperatively. A study using tepoxalin increased the duration of post-operative analgesia when given in combination with ropivacaine and methadone epidurally. The advantage of decreasing the isoflurane requirement and intra-operative analgesia effects were not found (Bosmans et al. 2012). NSAIDs, when used in CCL surgery alone, tend to be insufficient for controlling pain. To provide a satisfactory analgesic effect from NSAIDs, co-administration with other drugs such as local anesthetics or opioids or other techniques such as epidural blocks are required.

Dexmedetomidine is commonly used in small animals for its potent sedation and analgesic effects (Murrell & Hellebrekers 2005). The drug has been used in dogs with CCL disease by single injection and continuous rate infusion (CRI) techniques to maintain potent sedation during surgery (Campoy et al. 2012b; McCally et al. 2015). Dexmedetomidine has been used systemically in dogs receiving CCL surgery and prolonged sensory blocks to a greater degree than the local anesthetic alone. However, the requirement of rescue analgesia post-operatively was comparable to the dogs that did not receive dexmedetomidine. This indicated that dexmedetomidine could not provide sufficient post-operative analgesia on its own (Acquafredda et al. 2021). The use of dexmedetomidine CRI and propofol has shown sufficient sedation to

the point that hindlimb surgery can be performed under a peripheral nerve block. During the surgery, hemodynamic variables were all within the acceptable limits without any inotrope required. Severe hypoventilation was not observed, and the dogs were in sternal recumbency within 10 minutes after the CRI was stopped (Campoy et al. 2012b). The use of dexmedetomidine has been a significant part of sedation and anesthesia in dogs undergoing CCL surgery, but its use as a major analgesic agent may not be suitable. The drug has a short analgesic effect which may not be sufficient for all the surgical procedures and post-operative periods (Murrell & Hellebrekers 2005; Acquafredda et al. 2021).

Gabapentin is given preoperatively for soft tissue surgery. It has been shown to decrease post-operative rescue analgesia for 72 hours (Crociolli et al. 2015). However, when gabapentin was given pre-operatively for post-operative analgesia in amputation surgery, the analgesic effect was comparable to the group that received a placebo drug (Wagner et al. 2010). In addition, a study using gabapentin for post-operative pain in dogs undergoing intervertebral disc surgery also found a comparable analgesic effect with the control group (Aghighi et al. 2012). Using gabapentin as an analgesic adjuvant for post-operative analgesia is controversial. Post-operative analgesia seems to be sufficient for soft tissue surgery but not for surgeries involving high degrees of pain. The use of gabapentin in patients undergoing CCL surgery has not been reported. There is a potential to use gabapentin for post-operative pain, but it may have to be administered with other analgesia drugs.

Studies have compared the combination of tramadol and firocoxib in dogs who underwent TPLO surgery. The drugs were given orally one day before surgery. The results showed that pre-operative administration of only tramadol did not provide a good analgesic effect compared to firocoxib or the combination. Tramadol did not show a superior analgesic effect over firocoxib, and the synergistic analgesic effect of tramadol with firocoxib was not seen (Davila et al. 2013). Therefore, the use of tramadol for peri-operative analgesia in CCL surgery alone may not provide a sufficient analgesic effect. Using tramadol as a part of multimodal analgesia, combined with other drugs or techniques, may alleviate peri-operative pain. However, further studies are needed.

Continuous rate infusion (CRI) of analgesic drugs had been used in dogs undergoing surgery. The use of a single drug such as ketamine, morphine, or lidocaine for CRI in dogs has shown better peri-operative analgesia efficacy (Ortega & Cruz 2011; Guimarães Alves et al. 2014; Gutierrez-Blanco et al. 2015). However, no study compared analgesia effect using a CRI for CCL surgery. The use of a low dose combination of ketamine, morphine, and lidocaine (MLK) for CRI intraoperatively has shown to be effective. The combination can decrease inhalation anesthesia requirements without adverse hemodynamic effects and no difference of time to extubate (Muir et al. 2003; Wendt-Hornickle & Snyder 2016). As a result, MLK combination CRI in dogs with TPLO surgery showed lower requirement of isoflurane and provided a similar post-operative analgesic effect and sedation quality when compared to dogs that received epidural analgesia or received only morphine for premedication (Lewis et al. (2014). In another recent study, the use of MLK revealed a poorer post-operative pain score and worse sedation score when compared with a saphenous and sciatic nerve block (Kalamaras et al. 2021). As a result, using only MLK for CRI systemically may not be the best choice as a single analgesic technique for CCL surgery.

Systemic analgesia for CCL disease surgery is the most common approach used in veterinary medicine. It is effective, but the adverse effects observed may predispose to unwanted complications and limit its use (Boström et al. 2002; Hoelzler et al. 2005; Lafuente et al. 2005; Boström et al. 2006). Therefore, additional regional analgesia techniques have been incorporated as part of the multimodal analgesia and anesthesia approach for CCL surgery to improve pain management and reduce side effects and complications.

3.2 Regional analgesia techniques

Proper peri-operative pain management is essential for CCL disease surgical correction. Different regional analgesia techniques have been utilized to improve both anesthesia and analgesia. As mentioned, balanced or multimodal anesthesia and analgesia using systemic and regional techniques have become the new standard of care. Regional analgesia is defined as “insensibility to pain in a larger, though limited, body area usually defined by the pattern of innervation of the affected nerve(s)” (Tranquili & Grimm 2015). For CCL disease surgical correction, the anatomical surgical structure and innervation can be easily located.

The musculoskeletal and supplied nerves are discrete and uncomplicated to identify, and the surrounding structures can be used as a landmark. These allow regional techniques to relieve pain better and decrease systemic drug administration and its side effects. The use of local anesthesia to prevent sensory transduction, transmission, or modulation will prevent patients from perceiving peri-operative pain.

3.2.1 Intra-articular injection

Several nerve endings, including mechanoreceptors reside in the stifle joint. Almost 80% of them are nociceptive receptors responsible for pain transduction. Mechanoreceptors work by detecting postural changes to assist knee proprioception by changing the contraction of the muscle surrounding the joint to promote the balance of movement. The nociceptive receptors in the joint are commonly sensitized by chemical stimuli. Chemical stimuli are normally mediated via inflammation, especially during joint damage (Hong et al. 2019). CCL disease and surgery correction induce joint trauma and inflammation. Thus, managing pain at the level of the joint with direct intra-articular drug administration has shown to provide analgesia perioperatively (Sammarco et al. 1996; Hoelzler et al. 2005; Dutton et al. 2014). However, the technique primarily prevents pain arising from intra-articular structures and has limited effect on surrounding tissues or extra-articular tissue, typically involved during surgery (Campoy et al. 2015). Different drugs have been studied for intra-articular analgesia, including local anesthetics, opioids, α-2 agonists, and NSAIDs (Hoelzler et al. 2005; Moak et al. 2011; Soto et al. 2014; Di Salvo et al. 2016). Local anesthesia provides analgesia by inhibiting transduction and the generation and propagation of action potentials at the neuronal membrane (Yagiela 1991). Compared to opioids, intra-articular infiltration of local anesthetics provide better and prolonged analgesia postoperatively (Sammarco et al. 1996). On the other hand, local anesthesia drugs can cause chondrotoxicity, which has limited the use of intra-articular local anesthesia clinically (Sammarco et al. 1996; Grishko et al. 2010; Hennig et al. 2010). Intra-articular chondrotoxicity is associated with chondrocyte apoptosis and mitochondrial dysfunction (Yagiela 1991). Studies have shown that the severity of chondrotoxicity depends on the drug used. Lidocaine and bupivacaine cause more severe chondrotoxicity when compared to ropivacaine (Rao et al. 2014; Ickert et al. 2015). Chondrotoxicity due to local anesthesia is a dose- and time-dependent effect. An *in vitro* study

showed that cytotoxicity was found within 15 minutes after exposure to 1% lidocaine (Karpie & Chu 2007). In contrast, an *in vivo* study found that drug absorption was fast, which led to a decline in the concentration of local anesthesia after injection. The remaining drug concentration was reduced nine-fold in a healthy stifle joint and four-fold in an osteoarthritis joint within 30 minutes. This implied that a single local anesthetic injection is less likely to cause chondrotoxicity (Barry et al. 2015). However, the use of local anesthetics administered via this route is still of concern due to the unclarified chondrotoxicity effects in clinical settings (Sammarco et al. 1996).

The joint contains opioid receptors found in the periosteum, capsule, and synovium (Bergström et al. 2006). The density of these receptors increases when the joint becomes inflamed, which allows opioids to provide analgesia in the inflamed joint (van Loon et al. 2013). Therefore, opioids are another group of drugs commonly used for intra-articular analgesia with low chondrotoxicity effects (Jones et al. 2003; Ickert et al. 2015). Studies suggest that intra-articular opioid administration can provide analgesia comparable to epidural analgesia (Day et al. 1995; Sammarco et al. 1996; Keates et al. 1999; Vettorato et al. 2012). Nevertheless, a study in dogs showed that intra-articular morphine analgesia only lasted for approximately 30 minutes postoperatively, and the efficacy was lower when compared to local anesthesia drugs (Day et al. 1995; Sammarco et al. 1996).

The intra-articular administration of α-2 agonists has been shown to provide analgesia by acting directly on the α-2 receptor and as an adjuvant (Gentili et al. 1996). The adjuvant effect is associated with periarticular vasoconstriction, which delays absorption and prolongs the effects of other analgesic drugs such as opioids or local anesthesia. The combination of α-2 agonists with opioids or local anesthetics has been shown to have additional analgesic effects in animals and humans (Soto et al. 2014; Panigrahi et al. 2015; Ismail et al. 2017; Peng et al. 2018).

Overall, intra-articular techniques can provide analgesia but are insufficient to maintain patient comfort during and after surgery. In addition, limitations such as chondrotoxicity and short analgesia duration make intra-articular techniques less ideal as the sole mode for analgesia during CCL surgery.

3.2.2 Spinal and epidural analgesia

Spinal analgesia is a procedure performed by injecting an analgesia agent into the subarachnoid space. The space resides between the arachnoid matter and pia matter, where the cerebrospinal fluid is contained. The benefits of the technique include the objective landmark, the cerebrospinal fluid is observed when the needle reached the subarachnoid space; the onset and the efficacy are more profound because the local anesthetic solution is applied directly to the spinal cord, and the level or lateralization of the analgesic effect can be controlled by using hyperbaric analgesia and body position technique. However, potentially serious complications such as cardiac arrest, neurologic injury, or radiculopathy may limit the use of this technique (Otero & Campoy 2013). The spinal analgesia technique was applied in a patient that underwent TTA and TPLO surgery. The good post-operative pain quality, less intraoperative stress-related biomarkers, and smooth recovery quality were comparable to dogs who received a peripheral nerve block (Romano et al. 2016). Therefore, the technique tends to show the benefits of analgesic efficacy. The limitations of the technique and potential complications lead to infrequent use of the procedure.

Another technique commonly applied to patients undergoing CCL surgery is epidural analgesia (Otero & Campoy 2013). Epidural analgesia is a regional analgesia technique commonly used in human and veterinary medicine. The procedure provides analgesia when specific drugs are injected into the epidural space, which is the area between the dura mater and the wall of the vertebral canal. Direct administration of drugs to the spinal cord and nerve roots prevents sensory information from reaching the dorsal horn, which is associated with transmission and modulation processes for nociception (Hogan 2002; Gaynor & Mama 2009; Steagall et al. 2017; Grubb & Lobprise 2020). Analgesia is provided to caudal areas of the abdomen, pelvis, and pelvic limb (Otero & Campoy 2013). Studies have shown that epidural analgesia can decrease the requirements of intraoperative inhalation anesthesia and provide post-operative analgesia while decreasing pain scores. Epidural analgesia is considered an important component for multimodal and balanced anesthesia techniques during CCL surgery (Hendrix et al. 1996; Kona-Boun et al. 2006). (Day et al. 1995; Lewis et al. 2014). As drugs are administered directly into the spinal canal, multiple receptors and nerve targets give multiple drug options for epidural analgesia. Drugs clinically

reported for epidural analgesia in dogs include local anesthesia, opioids, α-2 agonists, neostigmine, and midazolam (Smith & Yu 2001; Hamilton et al. 2005; Kona-Boun et al. 2006; Campagnol et al. 2007; Bujedo 2014).

Local anesthesia drugs act by binding to voltage-gated sodium channels in spinal cord neurons and nerve roots. Binding prevents Na^+ influx and results in the prevention of depolarization. Local anesthesia drugs prevent and stop sensory and motor neuronal activity, including autonomic nervous system nerves. Pelvic limb innervation arises between L3 to S2 spinal cord segments. Thus, epidural analgesia with local anesthetics can provide complete analgesia to the pelvic limbs when the local anesthetic solution bathes these nerves. Due to the longer duration of effect, local anesthetic drugs commonly used for CCL surgery are bupivacaine and ropivacaine. Both bupivacaine and ropivacaine have an average duration of about 6 hours and will provide intra-operative and early post-operative analgesia. These local anesthetic drugs decrease the requirements for rescue analgesia and inhalation anesthesia during surgery. Even further, they decrease the requirements for post-operative rescue analgesia (McCally et al. 2015; Pownall et al. 2020). Nevertheless, the use of local anesthesia for epidural analgesia comes with inherent disadvantages. Local anesthesia drugs will induce motor dysfunction and paralysis of the pelvic limbs. (Gomez de Segura et al. 2009; Campoy et al. 2012a; Caniglia et al. 2012). The autonomic nervous system nerve roots from the sympathetic chain (T5 to L3 spinal nerves) may be desensitized with local anesthesia drugs. The result of this blockade is systemic hypotension (Martin-Flores 2013; Otero & Campoy 2013). Therefore, epidural analgesia performed with local anesthesia for CCL disease surgical repair is commonly used, but the side effects and disadvantages must be considered.

Other drugs commonly used for epidural analgesia with the idea of minimizing or avoiding motor dysfunction but maintaining analgesia are opioids and α-2 agonists. Opioid drugs bind to opioid receptors in the spinal cord. The activation of opioid receptors interferes with nociceptive impulses from sensory neurons and nerve endings. The epidural administration of opioid drugs is unlikely to induce motor dysfunction, as seen with local anesthesia drugs (Steagall et al. 2017). Studies have shown that morphine, buprenorphine, and oxymorphone can provide adequate analgesia in dogs when administered in epidural

space (Vesal et al. 1996; Smith & Yu 2001). Morphine has specific advantages because its hydrophilic property delays systemic absorption, resulting in a prolonged presence within the epidural space (Valverde et al. 1992; Steagall et al. 2017). Morphine epidural administration reduces halothane's minimal alveolar concentration (MAC) by almost 30% and provides post-operative analgesia (Valverde et al. 1989; Perez et al. 2013). The analgesia duration from epidural morphine administration has been reported to last up to 12-24 hours (Kona-Boun et al. 2006; Steagall et al. 2017). However, the analgesia observed from opioid administration in the epidural space is not complete enough for CCL disease surgical correction. The analgesia observed is vastly inferior when compared to local anesthesia administration. Thus, a combination of opioid and local anesthesia drugs provides better analgesia (Hendrix et al. 1996; Hoelzler et al. 2005; Adami et al. 2012; Campoy et al. 2012a; Lewis et al. 2014; Boscan & Wennogle 2016).

Similar to opioid receptors, the spinal cord dorsal horn contains α-2 receptors that inhibit sensory transmission and modulation (Gaynor & Muir 2009). The drug provides analgesia by inhibiting the afferent impulse at pre- and post-synaptic membrane hyperpolarization and inhibiting norepinephrine and substance P in the spinal cord. The α-2 agonist can also enhance the analgesic effect when administered with local anesthetics. The drug may escalate the analgesic effect by its vasoconstriction activity and direct inhibition of impulse propagation in the epidural space (Otero & Campoy 2013; Steagall et al. 2017). Dogs undergoing CCL surgery that received a combination of α-2 agonist and local anesthesia epidurally showed prolonged analgesia and better pain scores when compared to only local anesthesia (Branson et al. 1993; O & Smith 2013). However, the addition of α-2 agonist drugs to the epidural analgesia technique may cause further bradycardia, atrioventricular blocks and prolong the motor blockade with pelvic limb dysfunction (Rector et al. 1998; O & Smith 2013).

Ketamine has been reported to have analgesia effects when administered epidurally (Duque et al. 2004). When administered via the epidural route ketamine has an intrinsic activity of inhibiting sensory, motor, and sympathetic impulses. However, a previous study had shown damage of the spinal cord and nerves in humans and rabbits. This damage implies that ketamine should not be used by the epidural route

until there is evidence of its safety in dogs (Steagall et al. 2017). Furthermore, no studies have been done using ketamine epidurally for CCL surgery.

Neostigmine is a cholinesterase inhibitor. The analgesic effect, when administered epidurally, is associated with an increase of the acetylcholine concentration resulting in activating the muscarinic receptor in the spinal cord (Yaksh et al. 1985). The drug has reportedly been used in orthopedic surgery of the hindlimb in dogs. Studies have shown an analgesia effect when neostigmine is administered with opioids. Neostigmine can not provide adequate analgesia for orthopedic surgery alone, but only as an adjuvant with other drugs (Marucio et al. 2014). The use of neostigmine for peri-operative analgesia for CCL surgery has not been reported. Additional studies are required.

Midazolam is a water-soluble benzodiazepine that binds to the gamma-amino butyric acid (GABA) receptor to stabilize the transmembrane potential at the resting potential. This serves to decrease the excitability of the neuron. The drug binds to the receptor at the dorsal root nerve cells, particularly at the lamina II that play a role in the nociceptive and thermoceptive processes. There is a potential origin of analgesic effect at the spinal level (Reves et al. 1985; Bohlhalter et al. 1996; Prommer 2020). In human medicine, the drug has shown a benefit of an analgesic effect when given as an adjuvant with bupivacaine epidurally. The combination decreases the requirement of post-operative rescue analgesia (Nishiyama et al. 2002). In dogs, the epidural administration of midazolam had shown that the total amount of drug in cerebrospinal fluid was only 3% compared to the amount of drug in the systemic circulation. The time that the drug reached maximum concentration was 30 minutes after administration. This implied that the drug was poorly absorbed and fast distributed in the cerebrospinal fluid (Nishiyama et al. 2003). This may limit the use of the drug for the epidural route in dogs. In addition, the epidural analgesia failure rate reported in dogs can reach 32% (Iff et al. 2007; Iff & Moens 2010; Sarotti et al. 2015)

In summary, epidural analgesia is an effective and commonly used regional analgesia technique as part of the multimodal-balanced anesthesia embraced for CCL disease surgical repair in dogs. The potential technique complications such as inadvertent injection intravenously or into the subarachnoid space, CNS infection, contraindication in patients with skin infections or neoplasia at the injection site, contraindication

in patients with bleeding disorders, spinal cord damage, motor dysfunction (pelvic limb paralysis), and hypotension make epidural analgesia a less than ideal technique for unilateral CCL disease repair. (Hendrix et al. 1996; Jones 2001; Davies 2007; Otero & Campoy 2013; Campoy et al. 2015; Gulur et al. 2015)..

3.2.3Peripheral Nerve block

The purpose of a peripheral nerve block is to administer a solution in the vicinity of a peripheral nerve to temporarily block sensory and/or motor function (Campoy & Schroeder 2013). The regional anesthesia technique prevents pain transmission and nociceptive impulses from reaching the central nervous system. Local anesthetic drugs are the universal choice due to their mechanism of action acting on sodium channels present in the nerve axons preventing depolarization and propagation of nociceptive signals. As with any analgesia technique, nerve blocks have advantages and disadvantages. The benefits are adequate local or regional analgesia, minor systemic side effects, no contra-lateral limb dysfunction, and decreased requirement of other analgesic or anesthetic drugs. The disadvantages of nerve blocks are technique difficulty, failure rate, erroneous systemic drug absorption, motor dysfunction or paralysis of the limb and cost.

Nerve blocks have been used as a part of the multimodal anesthesia approach for CCL disease repair in dogs. It has been shown that dogs receiving nerve blocks require less intraoperative analgesia and less inhalation anesthesia. The use of nerve blocks provides better postoperative pain scores (Grubb & Lobprise 2020; Grubb et al. 2020). However, inconsistency in the literature exists with studies performing a variety of different blockade techniques and the details are discussed in the next chapter. Therefore, during my Ph.D., I developed and tested a nerve block technique for CCL disease surgical repair in dogs. In addition, I performed a cost analysis to determine the financial impact of ultrasound-guided nerve blocks in dogs.

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CHAPTER 4: NERVE BLOCKS FOR REGIONAL ANESTHESIA

As mentioned in chapter 3, nerve blocks for regional anesthesia are common techniques of injecting local anesthetic solution adjacent to a nerve which temporarily discontinues the conduction of action potentials and decreases nerve activity, pain transcription, and pain sensation (Campoy et al. 2015). This chapter will describe and discuss the detail of regional anesthesia and the application of the techniques for cranial cruciate ligament (CCL) disease surgical correction.

Peripheral nerve blocks have been in use since the 1880s. The first peripheral nerve block was reported in human patients using cocaine as the anesthetic drug for the ulnar nerve at the elbow. The analgesic effect was satisfactory and led to the development of other nerve block techniques (Kruisselbrink & chin 2015). In veterinary medicine, the first use of peripheral nerve blocks was reported in the 1940s; a paravertebral nerve block was used in cattle and later adapted for use in small animals (Schroeder 2013).

Peripheral nerve blocks have decreased anesthesia and perioperative analgesia drug requirements in veterinary species (Adami et al. 2016; Romano et al. 2016; Tayari et al. 2017). The reduced use of analgesic and anesthesia improves perioperative safety in dogs, by reducing complications such as bradycardia, hypotension, and the emergence of delirium/dysphoria with an overall better recovery from anesthesia (Grubb & Lobprise 2020). As a result, nerve blocks have become an important element for multimodal analgesia and anesthesia (Polomano et al. 2017).

Analgesia efficacy from the neve block depends on many factors. These include the local anesthetic properties, nerve structure, nerve type, and nerve block technique. The first factor affecting the efficacy of nerve blocks is the properties of the local anesthetic drug. Local anesthetic drugs are the major drug group used in peripheral nerve blocks because of their direct effect on nerve conduction. These drugs penetrate the lipophilic cell wall into the intracellular area and bind to the binding site at the inner pore of the voltage-gated sodium channel (Na_V)(Fozzard et al. 2011). This inhibits the action potential and nerve impulses, including nociception.

The local anesthetic structure consists of a lipophilic aromatic ring, intermediate ester or amide linkage, and terminal ending, all of which have an underlying effect on drug action. The potency of the block is associated with the drug pKa and lipid solubility. The terminal ending of the local anesthetic structure can change its form into tertiary or quaternary forms depending on the pKa property of the drug. The tertiary form is an un-ionized structure, which has lipid-soluble properties. The quaternary form is an ionized structure with hydrophilic properties. Formulations of local anesthetics are commonly in a water-soluble form that cannot penetrate neurons (Hogan 2008; Campoy & Schroeder 2013). A local anesthetic with low pKa has a greater amount of an un-ionized conformation in the physiological pH (pH=7.4), enhancing the drug's ability to pass through the intracellular area and shorten the block onset. For example, at physiological pH, mepivacaine (pKa 7.6) which has lower pKa, tends to have a shorter onset than bupivacaine (pKa 8.1). After the local anesthetic enters the neuron, the drug reforms to the quaternary structure, blocks the sodium channel, and prevents the action potential. Another factor that affects the onset of action is lipid solubility. Higher lipid solubility drugs rapidly diffuse through the cell membrane and have greater potency. However, the lipid solubility can sequester the drug in surrounding adipose tissue and myelin, slowly releasing the drug to the neural membrane, prolonging the duration of action and slowing the onset of action. Nevertheless, if a high drug concentration is injected, a greater number of molecules reach the neuron, which can override a prolonged onset of action. Duration of action is associated with the ability to bind to proteins. The greater the affinity for protein binding within the sodium channel, the longer the anesthetic block of the action potential. Duration of action can also be influenced by the vascularity of the injection site and the vasoconstrictor properties of the incorporated drugs. Higher vascularity of the injection area may enhance the absorption rate, resulting in a shorter duration of action. Therefore, combining a vasopressor with a local anesthetic formulation can delay the absorption of the drug from the target tissue (Becker & Reed 2012; Vadhanan et al. 2015; Barletta & Reed 2019).

The second factor that influences the block's efficacy is the nerve's character. Nerve fibers are composed of groups of fascicles organized in a parallel fashion. Fascicles are comprised of variable numbers of axons with different fascicle sizes. The axons within a fascicle are enclosed by connective

tissue, the endoneurium. Perineurium surrounds the primary fascicles groups. The perineurium has a tight junction and desmosomes to form layers and act as a barrier against diffusion particles. The interfascicular connective tissue layer, or epineurium, lies between and around the secondary fascicles and surrounds the nerve trunk (Barral & Croibier 2009). While performing a peripheral nerve blocks, the local anesthetic has to traverse the epineurium, endoneurium, and the critical barrier of the perineurium (Borgeat 2006). The thicker the perineurium, the more local anesthetic concentration is required to reach the steep concentration gradient for penetration (Taboada Muñiz et al. 2008). The thickness of the perineurium also dictates a greater concentration of local anesthetic to provide a shorter onset (Casati et al. 1999).

The third factor that affects the block's efficacy is the nerve fiber type. Different nerve fiber types respond to local anesthetic inconsistently. Local anesthesia that blocks only sensory nerves, spare motor nerves, and proprioception, is called a differential nerve block (Martin-Flores 2013). This ability may be advantageous if the block involves the respiratory movement muscles, that requires analgesia effect and still needs a capability to control the muscle movement. Gasser and Erlanger (1927) showed that small nerve fibers were more susceptible to desensitization by local anesthetics than larger nerve fibers. They found that the smaller diameter nerve fibers within the A-fiber group were blocked before the larger ones (Gasser & Erlanger 1927). This greater susceptibility to local anesthetic in smaller nerve fibers was observed in several studies (Matthews & Rushworth 1957; Nathan & Sears 1961; Franz & Perry 1974; Ford et al. 1984). However, this relationship is inconsistent in other types of nerve fibers (Heavner & de Jong 1974; Jaffe & Rowe 1996). Later, the susceptibility of the block was found in sensory rather than motor nerve fibers. (Butterworth et al. 1998; Vadhanan et al. 2015). The differential nerve block requires less local anesthetic than is generally used (Kii et al. 2014). The susceptibility among nerve fibers is abolished when high doses of local anesthesia are used (Gokin et al. 2001; Henkel 2001). As a result, performing a successful differential nerve block can be challenging (Kii et al. 2014).

In providing an effective peripheral nerve block, the fourth factor is injecting the local anesthetic agent close to the target area. To locate the appropriate point for injection, several guiding techniques are

used. The techniques include using anatomical landmarks, electro-stimulation nerve findings, and the ultrasound-guided technique. These techniques will be discussed later in this section.

In addition to analgesic efficacy, safety is an essential factor to consider while performing a peripheral nerve block. The safer the technique, the fewer the complications. Complications may occur from accidentally injecting local anesthesia solution into an inappropriate area or through needle puncture or laceration of surrounding tissue. Major complications consist of systemic toxicity and neurological injury. The first major complication, systemic toxicity, commonly occurs from the accidental injection of a local anesthetic solution intravenously, causing neurological and cardiac toxicity. Signs of neurological toxicity include muscle twitching, tremors, and seizures. Cardiological toxicity signs include tachycardia, hypotension, arrhythmias, cardiovascular collapse, and cardiac arrest (Jeng et al. 2010). The signs of toxicity depend on the local anesthetic used. For example, bupivacaine tends to cause cardiotoxicity before neurotoxicity, while ropivacaine causes neurotoxicity before cardiotoxicity (Dony et al. 2000; Campoy & Schroeder 2013).

The second complication from peripheral nerve blocks is nerve injury from trauma or pressure compression. Nerve trauma may be related to unintentional needle laceration or intraneural injection of the local anesthetic. Intraneural injection can increase intraneural pressure leading to injury or compression due to the confined space. This injury and compression may lead to a lack of ability of the nerve to conduct action potentials. Moreover, intraneural compression can exceed capillary occlusion pressure, preventing blood flow to the neuron and causing neuronal ischemia. Neuronal ischemia can also be generated from extraneural causes. The inadvertent puncture of the surrounding blood vessel can bring about hematoma, which compresses the neuron and prevents neuronal blood flow. Neuronal ischemia causes degenerative changes and fiber disconnection of the nerve (Hogan 2008; Campoy & Schroeder 2013; O'Flaherty et al. 2018). Because nerve block complications commonly involve laceration or inadvertent injection to the nerve, a technique for guiding the needle tip direction may enhance safety and decrease complications. The guiding techniques have been developed, including blind techniques using anatomical landmarks, electro-

stimulator nerve finding, and ultrasound-guided techniques. The following sections discuss guidance techniques for performing peripheral nerve anesthesia.

4.1 Blind techniques using anatomical landmarks

Blind anatomical landmark techniques were the first techniques developed to perform regional anesthesia in veterinary medicine. The techniques rely on knowledge of anatomical structures and the practitioner's perception while the needle is directed towards the target nerve (Campoy & Schroeder 2013). The technique only requires a needle and syringe containing local anesthetics solution, making it economical. The blind techniques provide effective analgesia for some procedures. It is commonly performed for dental procedures such as maxillary nerve and mandibular nerve blocks due to their prominent landmarks and easily identified locations (Gracis 2013). However, anatomical variations between patients may predispose to cause complications (Mahler & Adogwa 2008). For example, a report in a horse retrospective study showed the effect of anatomical variation that cause complication. A suborbital hematoma complication occurred while performing a maxillary nerve block due to variation in the horses' anatomy. The horse's maxillary tuberosity was shorter than normal, leading the needle to be repositioned caudally. The reintroduced needle lacerated a blood vessel, causing the hematoma (Tanner & Hubbell 2019). The blind techniques also have the limitation of not knowing the distance of the needle to the nerve, which may lead to blocking failure. The unknown proximity of the needle tip to the nerve may cause laceration or inadvertent injection of the local anesthesia solution to a non-target area. Therefore, the blind technique is not appropriate to apply in an area where the nerves are not easily identified or the desired location is difficult to locate as it can lead to ineffective blocks and predispose to complications (Rasmussen et al. 2006a; Thomson et al. 2021).

4.1.1 Use of anatomical landmark for cranial cruciate ligament surgery

Dallman (1980) first reported using peripheral nerve blocks for hindlimb surgery in dogs in the early 1980s. The regional anesthesia was performed using a blind approach for rear limb amputation in a dog. The anatomical landmark techniques were used for the caudal cutaneous femoral nerve, lateral cutaneous femoral nerve, and saphenous nerve. Analgesia was achieved even though the pain-alleviating

effects did not cover all portions of the limb (Dallman 1980). Analgesia results from Dallman's study were the starting point to use peripheral nerve blocks for hindlimb surgery (Kona-Boun et al. 2006; Campoy et al. 2012a; Gurney & Leece 2014; McCally et al. 2015).

Rasmussen et al. (2006b) improved the blind approach techniques to specifically block the saphenous, tibial, and common peroneal nerves to provide regional anesthesia for pelvic limb surgery. Cadaveric and live dog studies showed potential benefits. However, accidental intraneural nerve injection occurred. In addition, the technique did not provide efficient analgesia for CCL surgery (Rasmussen et al. 2006b; Rasmussen et al. 2006a).

4.2 Electro-stimulation nerve finding technique

During the past two decades, electro-stimulation nerve finding techniques have been used in dogs for regional anesthesia (Joubert 2002). Electro-stimulation of a nerve (ESN) provides objective information regarding needle tip proximity to motor nerves. This objective information may enhance the ability to appropriately inject the anesthetic agent adjacent to a target nerve, resulting in effective analgesia (Tsui & Hadzic 2007). The following section discusses how ESN works and the advantages and disadvantages.

4.2.1 Electro-stimulation of a nerve

Electro-stimulation nerve finding is a technique that relies on electrical current to identify a motor nerve. The electrical current is generated by the flow of electrons between electrodes (De Andres et al. 2005). The movement of electrons between electrodes generates electrical current (Tsui & Hopkins 2006). The electrical current stimulates the nerve by decreasing electrical differences between cell membranes , such as from -90 to -55 mV. Once the threshold is reached, the voltage-gated sodium channel opens, generating the action potential. The motor nerve is the target for electrical stimulation; the motor nerve response is the contraction of the corresponding innervated muscle(s). This response is used to confirm the needle tip's proximity to the target motor nerve (Tsui & Hadzic 2007). An important consideration is that pain information is carried via sensory nerves and not motor nerves. This is an intrinsic disadvantage to ESN for nerve blockade to provide analgesia and anesthesia. The ESN uses a pulse duration between 0.1-0.3 milliseconds to induce action potentials in motor neuron axons. If the pulse duration is greater than 0.3

milliseconds, there is a higher chance that the sensory nerve will be stimulated and cause discomfort if the patient is awake (Tsui & Hopkins 2006). The stimulus frequency is set at 1 to 2 Hz to distinguish muscle elicitation from spontaneous muscle twitching (Tsui & Hopkins 2006).

The amount of the electrical current is determined by the proximity of the insulated needle tip to the nerve. Coulomb's law can explain this:

$$I_t=K(I/r^2)$$

I_t refers to the intensity of the electrical current at the target nerve, K refers to the constant of the electrical properties of the medium that the current is passing through, I refers to the intensity of the electrical current at the source (needle tip), and r is the distance between the electrical source (needle tip) and the target nerve (De Andres et al. 2005; Urmey 2006). As shown by the equation, an electrical current at the electrical source must be very high if the distance of the electrode is far from the target nerve because the relationship of the distance is an inverse of the square. A lower electrical current is necessary to generate an action potential if the needle tip is near the target nerve. While performing a nerve block, the initial setting of the stimulation current is 1-2 mA and gradually decreases when the needle tip gets close to the target nerve. Motor activity, observed when the electrical current is 0.5 mA, indicates adequate proximity of the needle tip to the nerve to provide a 95% successful nerve block (Gurnaney et al. 2007). It has been suggested that when the current is below 0.2 mA and motor activity is still found, the needle tip may be located within the nerve, and intraneural injection can occur (Hadzic et al. 2004; Sung 2004; Gurnaney et al. 2007; Robards et al. 2009; Portela et al. 2013a; Shariat et al. 2017). Therefore, understanding the electrical current adjustment technique while performing nerve blocks is essential for appropriate blockade.

The peripheral nerve block with ESN requires a specifically designed needle to connect to electrical nerve localizer devices. The designed needle is insulated except for the tip of the needle. The insulation allows for the electrical current to be released only at the tip of the needle as a guide to find the desired motor nerve.

4.2.2 Application of electrical nerve stimulation for cranial cruciate ligament surgery

The electro-stimulation nerve finding technique increases specificity and success. In order to get effective analgesia from using ESN, the practitioner needs to aim for specific nerves that supply the target area. The major nerves associated with CCL surgery are the femoral and sciatic nerves. The femoral nerve is derived from the lumbar plexus, which plays a role in the pelvic limb and provides both the motor and sensory nerve branches. The saphenous nerve is the sensory branch of the femoral nerve and the target for the nerve block. The saphenous nerve is formed from the cranial belly of the femoral nerve, and it branches before it leaves the iliopsoas muscle, which resides in the inguinal area. Because the saphenous nerve is close to the femoral nerve, the contraction of the quadriceps muscle corresponding to the femoral nerve is used as a surrogate when ESN is used to indicate that the needle tip is adjacent to the target nerve (Mahler & Adogwa 2008). The saphenous nerve supplies the middle and distal medial surface of the skin around the femur (Cox & Riedesel 1997). In addition to the femoral nerve, the sciatic nerve is another target nerve that must be blocked for better analgesia (McCally et al. 2015). The sciatic nerve innervates the pelvic limb and the stifle joint from the caudolateral aspect and consists of motor and sensory nerves. Therefore, when using ESN, the dorsiflexion or plantar extension of the foot was the response when the nerve was elicited (Campoy et al. 2012a).

Campoy et al. (2012a) introduced techniques for using ENS that aimed at the femoral and sciatic nerves. The femoral-saphenous nerves were targeted at the femoral triangle in proximity to the inguinal area. The sciatic nerve was the target below the line drawn from the greater trochanter and ischiatic tuberosity (Campoy et al. 2012a). These techniques were applied in the clinical studies in dogs who underwent tibial plateau leveling osteotomy (TPLO) surgery. The nerve blocks provided intraoperative and postoperative analgesia and postoperative pain scores comparable to epidural injections (Campoy et al. 2012a; Caniglia et al. 2012; McCally et al. 2015; Boscan & Wennogle 2016). A superior result of the peripheral nerve blocks was a lower incidence for urinary retention (Campoy et al. 2012a). Studies suggest that ESN guidance for femoral and sciatic nerve blocks can be used interchangeably with epidural analgesia (Campoy et al. 2012a; Caniglia et al. 2012; McCally et al. 2015).

A lumbar plexus block with ESN has been performed using both multiple and single-injection techniques. The multiple-injection technique uses ESN to guide the needle to inject a local anesthetic at the lumbar nerve trunk near the nerve root that supplies the pelvic limb together with blocking the sciatic nerve (Portela et al. 2008). Studies performed by Campoy et al. (2012b) and Congdon et al. (2017) showed multiple injections for a lumbar block and sciatic nerve could prevent the need for additional intraoperative analgesia for 86.6% of dogs that received pelvic limb surgery, including stifle surgery. While the single-injection technique that approaches the lumbar plexus revealed a lower requirement of intraoperative analgesia for 76% and good postoperative analgesia results in dogs that underwent stifle surgery (Portela et al. 2013b; Vettorato et al. 2013; Romano et al. 2016). These techniques were performed by only a one-time injection for the lumbar plexus block, but complications associated with contralateral limb paralysis were found, which may result from the extradural spread of local anesthesia (Vettorato et al. 2012; Vettorato et al. 2013). The lumbar plexus with ESN approach had shown a benefit for good analgesia efficacy, indicating that the lumbar area was an appropriate area for performing the lumbar plexus block with ESN for stifle surgery. Contralateral paralysis was a potential complication that developed at this area which the blindness of the ESN technique may cause.

Overall, peripheral nerve blocks with ESN showed benefits with a high degree of success for stifle surgery (Campoy et al. 2012a; Portela et al. 2013b; Vettorato et al. 2013; Romano et al. 2016; Congdon et al. 2017). However, the ESN technique has safety concerns and a degree of failure. The ESN informs on the proximity to the target nerve but does not provide information regarding the needle travel direction or other structures. This affects technique safety concerning inadvertent puncture or penetration of critical structures. Inadvertent puncture and injection of local anesthetic intraneural can create nerve damage by causing myelinated fiber loss, extensive fibrosis, and collagen disarray (Farber et al. 2013). Block failure can also occur with nerves moving away from the needle while the local anesthesia solution is injected. In this circumstance, the loss of motor activity while eliciting electrical nerve stimulation does not always indicate block success. Therefore, visualization while performing nerve blocks is an important technique evolution.

4.3 Ultrasound-guided regional anesthesia

Ultrasonography is an imaging technique often used in human and veterinary medicine to visualize soft tissue structures within the body in a real-time fashion. The ultrasound image is obtained from high-frequency sound waves. Ultrasound can aid peripheral nerve blocks by enhancing efficacy and safety when visualizing the needle tip and surrounding areas while traveling to the target nerve. How ultrasound can be applied to perform peripheral nerve blocks is discussed below.

4.3.1 Basic physics of ultrasonography

Understanding the basic principles of ultrasonography and how the image is created can help a practitioner obtain appropriate pictures while performing regional anesthesia. Ultrasound is a high-frequency mechanical wave that humans cannot hear (Mattoon & Nyland 2015). Ultrasound is generated from the vibration of the energized piezoelectric crystal in the transducer probe. The image is obtained from the waves that echo back to the transducer. The echo waves are translated into an image and displayed as ultrasonography (Sites et al. 2007b; Mattoon & Nyland 2015). The image is developed based on the velocity of ultrasound waves that travels through different materials (Evans 2008; Mattoon & Nyland 2015). The velocity of the sound wave is enhanced when the tissue has greater stiffness. For example, a sound wave has a higher velocity when traveling through bone (4080m/sec) than soft tissue (1,540 m/sec), which is less dense than bone. Tissue has a sound transmission characteristic, which is called acoustic impedance. Each tissue has an individual acoustic impedance based on tissue density and velocity. When echo waves are reflected back to the transducer in the area where the tissues have different acoustic impedance, adjacent structures are differentiated in the ultrasound image. The small details of the object, such as the parenchymal tissue, are created from the scattering echoes, which travel back to the transducer (Evans 2008; Mattoon & Nyland 2015). The image's fine details can enhance the ability to quantify the proximity of two objects and how they are distinguished, which is called resolution. A better resolution image is associated with the higher frequency ultrasound wave. However, the better image from the high-frequency wave has a trade-off. The object absorbs the energy of the high-frequency wave to a greater degree than the lower frequency wave. This quantity of energy from the sound wave that the tissue can absorb while traveling is called

intensity. Intensity is decreased along the way as the sound wave encounters the tissue. The loss of intensity is called attenuation. Therefore, high-frequency ultrasound waves have a greater attenuation but penetrate the tissue less deeply, which results in good resolution but shallow depth in the ultrasound image (Evans 2008; Mattoon & Nyland 2015). This indicates that the image's depth depends on the ultrasound frequency. If the target area is deep, the ultrasound frequency required is low, which may decrease the resolution (Shilo et al. 2010). Therefore, a transducer with the highest frequency that allows adequate penetration of the selected depth is recommended in ultrasound-guided regional anesthesia (Mattoon & Nyland 2015). Modern transducers have a broad bandwidth function that can operate multifrequency ultrasound waves. A broad bandwidth transducer is beneficial for regional nerve blocks because it can provide near and far fields of view from the same transducer, and its adjustability can improve the resolution of images for superficial structures (Mattoon & Nyland 2015).

4.3.2 Ultrasound image in a peripheral nerve block

Ultrasound-guided techniques increase safety and analgesic efficacy by providing the ability to identify the nerve's image and surrounding structures in ultrasonography (Barral & Croibier 2009). The nerve is characterized as round or oval hyperechoic (bright) structures in the short axis or a transverse section. Hyperechoic structures are the surrounding epineurium and the perineurial fatty tissue. A hypoechoic (dark) area, the nerve's internal tissue or fascicular structure, may be observed. With transducer manipulation, separation by hyperechoic septae can appear as a "honeycomb" texture in some large nerves. These septae are formed from the interfascicular epineurium (Kele 2012; Seco et al. 2013). A hyperechoic line and disruption of continuity by multiple hypoechoic stripes is termed a fascicular pattern (Marhofer et al. 2005).

Common nearby structures are blood vessels, muscle, fascia, fat, and bone during an ultrasound-guided peripheral nerve block. Muscle is characterized as a heterogenous striated structure consisting of a hypoechoic appearance from muscle fibers and hyperechoic patterns from the fascia, connective tissue, and fat. Muscle appears as a marbled image in transverse sections and homogenous fine parallel echoes in the longitudinal axis. The surface of the bone is characterized by a hyperechoic line associated with the high

reflection of the ultrasound wave (Seco et al. 2013). A vital structure characterized similarly to the nerve is blood vessels. Color Doppler flow techniques can differentiate blood flow direction and speed from nerves. Doppler ultrasonography is an image derived from the physical interaction of ultrasound and flowing blood. The flow of blood cells can be detected from the reflection of the ultrasound while it moves toward or outward from the transducer. The doppler technique differentiates blood vessels from other tubular structures, particularly target nerves (Sites et al. 2007b; Seco et al. 2013; Mattoon & Nyland 2015). A good understanding of the surrounding structures and the nerve is essential. Identifying each structure objectively with ultrasonography can prevent accidental needle puncture and provide an effective nerve block.

Another critical point for ultrasound-guided regional anesthesia is needle visualization. Sound wave reflects needle patterns. Ultrasonography visualizes the needle by its artifact property, termed reverberation. Reverberation occurs when the ultrasound beam repeatedly bounces between two highly reflective surfaces. The sound wave bounces back and forth between the transducer and the needle, creating multiple echoes from an ultrasound pulse. Reverberation depends on the penetrating power and sensitivity of the transducer. Visualization is increased when the beam is maximized to reflect the transducer. This can be achieved by placing the needle at a perpendicular angle to the ultrasound beam (Sites et al. 2007a; Mattoon & Nyland 2015). However, it is difficult to maintain the needle parallel with the transducer surface. Visualization of the needle may decrease while the needle travels. This limitation can be minimized using specific ultrasound softwares to steer the ultrasound beam precisely perpendicular to the needle and enhance the needle's brightness. These softwares allow regional anesthesia to be accomplished more easily (Viscasillas et al. 2013).

Moreover, modified needles have been designed to enhance the ultrasound signal. Polymer coating or embedding a pattern on the shaft and needle tip can increase needle visualization. These techniques increase the reflection ability, thereby enhancing the visualization of the needle (Gottlieb et al. 1998; Culp et al. 2000; Hebard & Hocking 2011). Studies in human medicine have shown that an echogenic needle can enhance the visibility of the needle tip, which increases block safety and efficacy (Hebard & Hocking 2011).

While using ultrasound guidance, there are two needle insertion directions: the in-plane and out-of-plane techniques. The in-plane technique orients the needle parallel to the long axis of the transducer probe. This technique allows visualization of the shaft and tip of the needle while directed toward the object. The trajectory of the needle is observed, allowing the user to avoid important structures. The out-of-plane technique orients the needle perpendicular to the long axis of the transducer probe (Kumar et al. 2007). This technique forces the practitioner to make assumptions about the shaft and the tip of the needle while performing the procedure. The advantage of the out-of-plane technique is that it provides a short distance for advancement suitable for small areas and causes less discomfort (Fredrickson & Danesh-Clough 2013; Meiser et al. 2016). If the insertion area for the needle is limited, the out-of-plane technique may be better, but if the insertion area is sufficient to direct the needle, the in-plane technique tends to be best to visualize the needle track and important structures.

The ultrasound provides a real-time visualization, which is advantageous when applying the technique to inject a local anesthetic adjacent to the target nerves. The ultrasound is beneficial for guiding the needle to the correct position, which increases the block's efficacy. The ultrasound-guided technique can decrease the duration of the procedure compared to the block that uses other guidance. This decreased time is associated with the visualization of the needle and surrounding area, and it reduces tissue damage from the ability to avoid the important structure. The real-time image allows the practitioner to redirect the needle tip to the appropriate target area. In addition, the doppler technique in the ultrasound allows the blood vessel and nerve to be differentiated, enhancing the block's safety (Seco et al. 2013). The ultrasound provides good analgesic efficacy and safety for the nerve blocks (Hopkins 2007). Therefore, ultrasound-guided regional anesthesia has been considered the gold standard for performing peripheral nerve blocks in human and veterinary medicine (Hopkins 2007; Schroeder 2013; Falyar 2015). However, ultrasound-guided peripheral nerve blocks also have disadvantages in terms of cost and personnel training. The cost for an ultrasound unit ranges between 20,000 and 80,000 USD, depending on the available options. The use of ultrasound also requires a trained practitioner in ultrasonography (Kim et al. 2014).

During my Ph.D. and dissertation, I developed and studied an ultrasound-guided with ESN technique to improve anesthesia and analgesia in dogs undergoing TPLO surgery. The ultrasound was used for the benefits of its visualization, and ESN was used to confirm the proximity of the needle tip and the target nerves. Therefore, I hypothesized that peripheral nerve blocks would reduce the requirements for anesthesia and analgesia and decrease the incidence of complications. In addition, because of the of high-cost that may be an obstacle for veterinarians and clients, I assessed the cost of performing these techniques to determine whether the technique was reasonable to use in clinical practice.

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CHAPTER 5: EFFICACY OF LUMBAR PLEXUS AND SCIATIC NERVE BLOCKS FOR TIBIAL PLATEAU LEVELING OSTEOTOMY[1]

Dogs suffering from cranial cruciate ligament (CCL) disease are commonly treated with surgery. In the USA, tibial plateau leveling osteotomy (TPLO) is the most common surgical treatment of choice, with nearly 30,000 surgeries performed per year. (Duerr et al. 2014; von Pfeil et al. 2018). As mentioned in Chapters 1 and 2 in detail, these surgical procedures involve significant intraoperative and postoperative pain (Slocum & Slocum 1993; Hoelzler et al. 2005; Boscan & Wennogle 2016; Romano et al. 2016). My Ph.D. project objective and goal were to improve pain management for these surgical procedures intraoperatively and postoperatively without creating significant financial burden to veterinarians and dog owner or clients. As previously discussed, perioperative analgesia is essential for a good operative outcome and to reduce the cost of care (Joshi et al. 2014; McCally et al. 2015; Saporito et al. 2019). In addition, proper perioperative analgesia will prevent chronic pain development or maladaptive pain (Molsa et al. 2013; Molsa et al. 2014).

As discussed in chapter 3, systemic administration of analgesia has been the standard of care for CCL rupture surgery repair in dogs. The use of opioids and NSAIDs provide effective analgesia, but the undesirable effects such as bradycardia, respiratory depression, vomiting, urinary retention, emergence delirium, dysphoria, gastric ulcers, nephrotoxicity, and hepatotoxicity are considerations when using higher doses to achieve adequate analgesia (Pettifer & Dyson 2000; Hoelzler et al. 2005; Camargo et al. 2011; Lewis et al. 2014; Berry 2015; Bini et al. 2018). To reduce the dose of systemic analgesics and decrease the chances of developing complications, balanced anesthesia and analgesia with other drugs or techniques are suggested (Fowler et al. 2003; Deneuche et al. 2004; Bergmann et al. 2007; Gruet et al. 2011; Bufalari et al. 2012). Additional techniques such as epidural analgesia or peripheral nerve block have been studied

[1]Warrit K, Griffenhagen G, Goh C, Boscan P. Comparison of ultrasound-guided lumbar plexus and sciatic nerve blocks with ropivacaine and sham blocks with saline on perianesthetic analgesia and recovery in dogs undergoing tibial plateau leveling osteotomy surgery. *Vet Anaesth Analg* 2019;46:673-681.

in CCL rupture surgery patients. Epidural analgesia provides effective analgesia, muscle relaxation, and comfort during recovery for dogs undergoing CCL rupture surgery. However, side effects, including intraoperative hypotension, bilateral pelvic limb paralysis and urinary retention, present undesirable complications to consider (Hoelzler et al. 2005; Caniglia et al. 2012; Adami et al. 2016). Peripheral nerve blocks are another option to control perioperative pain during CCL rupture surgery and repair. The technique was originally described as using anatomical landmarks to guide the nerve blocks. The analgesia results were inconsistent (Dallman 1980; Rasmussen et al. 2006b; Rasmussen et al. 2006a). To increase the technique's sensitivity and specificity, electro-stimulation of the nerve (ESN) was added to better locate the nerves, as described in Chapter 4. This technique decreased systemic anesthesia and analgesia drug requirements, stress-related biomarkers, and improved perioperative pain management (Campoy et al. 2012a; Boscan & Wennogle 2016; Romano et al. 2016). Nevertheless, the ESN technique only provides information on the proximity of the needle to the nerve. It does not provide information while the needle travels through the body or area of local anesthesia diffusion or the needle's proximity to sensory nerves. ESN only works with motor nerves as ESN stimulates the innervated motor muscle. For CCL repair, the saphenous nerve is mostly a sensory nerve with little to no motor muscle innervation. This may lead to accidental damage of important structures when the needle travels, erroneous local anesthesia diffusion, technique delay, and decreased sensitivity-specificity for sensory nerves (Brown 2008; Vettorato et al. 2012; Vettorato et al. 2013; Kim et al. 2014). Real-time visualization via ultrasonography tends to resolve these complications, as described in Chapter 4. The ultrasound-guided technique provides real-time visualization to encircle nerves with local anesthesia and avoid needle puncture of inappropriate structures. Therefore, ultrasound-guided techniques were introduced to enhance efficacy, sensitivity, and safety. My Ph.D. dissertation studied an ultrasound-guided technique to improve anesthesia and analgesia in dogs undergoing tibial plateau leveling osteotomy surgery to correct CCL disease. As mentioned in Chapter 4, the hypothesis was that peripheral nerve blocks would reduce the requirements for anesthesia and analgesia and decrease the incidence of complications. The 2nd study objective assessed the cost of performing these techniques in a veterinary practice.

The lumbar plexus and sciatic nerve were the targets for regional analgesia as they provide most of the innervation to the stifle area (McCally et al. 2015; Tayari et al. 2017). The details of the invention of the novel ultrasound-guided technique used in this study are discussed in the following section.

5.1 Ultrasound guided regional analgesia for the stifle

Ultrasound guidance regional analgesia for CCL rupture surgery was first described for the femoral nerves. A 13-4 MHz linear transducer was used to visualize the femoral nerve at the inguinal skin crease area, cranial to the pectineus muscle. Visualization of the femoral nerve was only 50% with in-plane technique insertion. It was difficult to create a "doughnut sign," and the technique's success was as low as 33% (Echeverry et al. 2010). Later, the technique was modified using a higher frequency ultrasound transducer probe (14-10 MHz) and changing the leg's position to the uppermost. All cases resulted in the blocking of sensory and motor nerves in this *in vitro* study (Costa-Farré et al. 2011). Ultrasound-guided femoral nerve block at the inguinal area, together with a sciatic nerve block, were used in dogs that underwent surgery on the stifle. During the operation, the dogs received heavy sedation with dexmedetomidine and propofol continuous rate infusion (Campoy et al. 2012b). This indicated that only the block at the femoral and sciatic nerves tended to be insufficient for complete stifle surgery analgesia. In addition, as mentioned in chapter 2, the nerves involved in CCL surgery are not limited to the saphenous and sciatic nerves. Other nerves such as the obturator or lateral cutaneous femoral nerves are also engaged. Therefore, blocking only the saphenous nerve may not be sufficient to control CCL surgical pain. The ultrasound-guided nerve block in the lumbar plexus method was designed to recruit additional nerves (Evans 1993; Campoy et al. 2008; Portela et al. 2008; Portela et al. 2010; Portela et al. 2013; Tayari et al. 2017).

The lumbar plexus with ultrasound guidance was chosen as the target area to perform the block. This area has a tangible surface landmark with good differentiation between the plexus and muscle under the acoustic window (Echeverry et al. 2012; Graff et al. 2015; Mogicato et al. 2015). The psoas muscle has a well-confined fascia that allows the distribution of the local anesthetic commonly contain within the muscle group and the plexus (Mannion et al. 2005). Moreover, blood flow to the psoas muscle is sparse,

which can decrease the absorption of the local anesthetic solution and prolong the effect of the regional analgesia. The lumbar plexus block using ultrasound was developed to optimize the efficacy and safety of the technique. The first cadaveric study was performed by placing the ultrasound transducer probe on the abdomen slightly cranial to an inguinal nipple and oriented perpendicular to the midline with the cadaver in dorsal recumbency. The target lumbar plexus was in the short-axis view within the psoas major muscle. In the image, the psoas major muscle has a hypoechoic property surrounding the nerve (hyperechoic oval structure), creating greater contrast between the two structures and allowing the nerves to be well-identified. The needle was inserted from the lateral side of the body using the in-plane technique with 0.2 mL/kg of staining solution. The staining covered the lumbar plexus at a distance greater than 2 cm, which was sufficient to include the femoral and obturator nerves in every dog. The 2 cm staining distance indicated that the solution was sufficient to provide an analgesic effect (Echeverry et al. 2012). This lumbar approach was used in live dogs with 0.5% bupivacaine. The block at this approach provided a short 15-minute onset, with a sensory and motor block duration of 10 hours (Shimada et al. 2017). To increase the efficacy of this lumbar plexus nerve block, Mogicato et al. (2015) suggested that the external iliac artery, which resides near the femoral nerve, could be used as a landmark under ultrasound guidance. It was also suggested to block the nerve by using the 7^{th} lumbar vertebra as a transducer position landmark. Using this landmark location increased the possibility of blocking the femoral and obturator nerves with dye 0.1 mL/kg (Graff et al. 2015). Another study placed the ultrasound transducer probe at the area ventral to the iliac crest and aimed for the lumbar plexus in the psoas major. The needle was directed from the lateral part of the body. This lumbar plexus approach with sciatic nerve block was used in dogs that underwent TPLO surgery. The approach showed a high success rate of 90% based on the intraoperative fentanyl requirement and provided adequate analgesia in the early postoperative period (Tayari et al. 2017).

The lumbar plexus block technique used in the present study was modified for effective and safe regional analgesia based on these mentioned studies. The technique was modified by positioning the dog in the lateral recumbency (Graff et al. 2015). The transducer probe was placed from ventral of the body part (Tayari et al. 2017). The ultrasound transducer probe was aimed towards the lumbar plexus in the psoas

major at the L6 position using the iliac crest as an anatomical landmark, following Graff et al. (2015). The external iliac artery was used as a landmark under the acoustic window (Mogicato et al. 2015). The needle was inserted from the lateral part of the body to create the in-plane approach (Echeverry et al. 2012). The local anesthesia was injected surrounding the plexus to create a "doughnut sign"(Campoy et al. 2010).

Ultrasound-guided regional analgesia at the lumbar plexus showed the ability to provide good perioperative analgesia. However, a previous study had shown the potential to enhance the analgesic efficacy of CCL surgery by blocking the nerve derived from the lumbar plexus and the sciatic nerve (McCally et al. 2015). The sciatic nerve block can be performed along the area where the nerve travels. Therefore, several approaches were introduced. The first technique used a parasacral approach. The technique aimed to block the nerve in the most proximate area where the nerve diverges. A transducer probe was placed at the level of the greater trochanter and followed the sciatic nerve proximally to the area where the nerve crosses the ilium, beneath the sacroiliac joint. In this area, the thick fascial structure covering the sciatic nerve prevents local anesthesia from encircling the whole nerve and results in a low success rate of 67% (Shilo et al. 2010). The complete surrounding of the nerve with an anesthetic injection or "doughnut sign" was used as a predictor of a successful block in the previous study (van Geffen & Gielen 2006). Another approach was studied to enhance the ability to block the sciatic nerve. The technique was designed to place the transducer probe to be immediately distal to the greater trochanter of the femur and ischiatic tuberosity. In this area, it was feasible to observe the cross-sectional axis image of the sciatic nerve to use an in-plane approach for creating the "doughnut sign." This ultrasound probe placement allowed a larger acoustic window to approach the sciatic nerve to perform the block (Echeverry et al. 2010). In the present study, the sciatic nerve block applied the technique from Echeverry et al. (2010). This technique has the potential to provide good real-time visualization of the sciatic nerve while the local anesthetic encircles the nerve.

This novel ultrasound-guide lumbar plexus and sciatic nerve block was developed to enhance the analgesic efficacy and the safety for the dog undergoing TPLO surgery. The following section describes the details of how the study was constructed.

5.2 Materials and methods

Before initiating the clinical study, approval was obtained by the Colorado State University Institutional Animal Care and Use Committee and Clinical Board Review Committee (09-1299A). The owners of all dogs included in the study signed a consent form, allowing their dogs to participate in the study. Dogs with unilateral CCL rupture and those scheduled for TPLO surgery were included in this study. Each dog was to receive TPLO surgery by the same board-certified surgeon to maintain surgical technique and tissue handling consistency. The TPLO surgery technique was performed following the description of Kowaleski et al. (2012) to make sure that the dogs received the same surgical technique. Dogs undergoing TPLO surgery for bilateral CCL rupture were not enrolled in the study due to the greater potential risk of complications (Priddy et al. 2003). Bilateral TPLO surgery causes pain in both hindlimbs affecting the dogs' ability to walk, confounding the evaluation of the dogs' pain and ability to bear weight. Dogs with complete blood cell counts and blood chemistry values within the normal reference ranges, with body condition scores of 5-6/9, and an American Society of Anesthesiologists status of II were enrolled. The health of the enrolled dogs before surgery needed to be similar to decrease the variability of drug dose requirements. Dogs with health conditions may require lower doses of anesthesia and analgesia drugs than healthy animals, confounding the study's investigation outcomes. Dogs with the following conditions were excluded from the study. First, dogs with dermatological lesions in the area intended for regional analgesia were excluded to prevent an ascending skin infection (Campoy & Schroeder 2013). Second, any dog receiving behavior-modifying drugs that could impact the study's sedation and analgesia scores were not enrolled. Behavioral modifying drugs should have been discontinued at least four weeks before surgery and study day (NADA141-27 2007:11; Trepanier 2013). Third, dogs that received a surgery technique that deviated from the standard TPLO procedure were not included to ensure that surgical stimulation was similar for all dogs in the study.

The study was designed as a randomized, prospective, blinded clinical trial. The sample size was calculated using a study power and alpha value from a previously published study. Power was calculated from 1-β, and β stands for type II error, which was the probability of accepting the null hypothesis when

false. The alpha value is the probability of rejecting the null hypothesis when it is true. The sample size of this study was based on Congdon et al. (2017) study. The study compared the effect between groups of dogs that received regional analgesia with and without local anesthesia to the lumbar and parasacral plexus for pelvic limb amputation. The calculation used a power of 80% and an alpha value of 5% to quantify the sample size. A total of 20 dogs were enrolled in the study. A minimum of 10 dogs per group were necessary to detect a difference in the postoperative visual analog pain scale (VAS).

Each dog in the study was randomly allocated to one of two groups by pulling the assigned group allocation from a sealed envelope. Dogs that received lumbar plexus and sciatic nerve blocks with ropivacaine were assigned to the regional analgesia (RA) group. Dogs that received the same block technique with sterile 0.9% saline were designated as the control (CON) group. Dogs in the RA group received ropivacaine 0.75 mg/kg (0.5% Naropin), which equivalent to 0.15 mL/kg, for the lumbar plexus block. The same dose of ropivacaine (0.75 mg/kg or 0.15 mL/kg) was used for sciatic nerve block. The total dose of ropivacaine that the dog received was 1.5 mg/kg (0.3 mL/kg). Dogs in the control (CON) group received sterile 0.9% saline using a volume equivalent to ropivacaine in the RA group (0.3 mL/kg) administered to encircle the lumbar plexus and sciatic nerve, which were visualized with ultrasound for confirmation.

5.2.1 Regional analgesia or nerve block technique

The nerve block techniques performed in this study were performed under the guidance of ultrasonography. Ultrasound-guided regional analgesia is a technique where the nerve block is performed under the visualization of the needle, target nerve, and adjacent structures. Ultrasound provides a real-time image that allows visualization of needle movement and local anesthetic spread. Ultrasound-guided regional analgesia promotes the accurate deposition of a local anesthetic to immediately encircle the target nerve and avoid damage to critical structures, such as blood vessels and adjacent organs (Marhofer et al. 2005; Kele 2012; Seco et al. 2013).

5.2.1.1 Lumbar plexus regional analgesia

In the present study, to desensitize the nerves known to innervate the stifle area, regional analgesia for the lumbar plexus and sciatic nerve was performed while the patient was under anesthesia and in lateral recumbency. Regional analgesia was performed in the uppermost leg with the limb in a neutral position. Hair was clipped for the blocks and surgery. The skin was aseptically prepared with 2% chlorhexidine in alcohol (ChloraPrep®). Ultrasound was used in the study to visualize the needle, target nerve, and adjacent structures. Ultrasound provided a real-time image and allowed observation of the needle's movement and the spreading of the local anesthetic. This allowed the veterinarian to encircle the nerve appropriately and decrease the potential for damaging surrounding structures (Marhofer et al. 2005; Kele 2012; Seco et al. 2013). The ultrasound images were obtained with a 15-6 MHz linear transducer. (Figure 5.1; SonoSite M-Turbo, FUJIFILM SonoSite, Inc., WA, USA). The broad bandwidth linear ultrasound can operate multifrequency ultrasound waves that provide near and far fields of view from the same transducer. Its adjustability can improve superficial structures' image resolution (Mattoon & Nyland 2015). The enhanced needle visualization mode was turned on to increase the ability to identify the needle during the procedure (Viscasillas et al. 2013).

For the lumbar plexus block performed in this study, the ultrasound transducer was aimed at the lumbar plexus in the transverse (short axis) orientation. The ultrasound transducer probe was placed perpendicular to the midline and cranial to the iliac crest at the L5-L6 level. The external iliac artery was used as a landmark in the acoustic window to identify the lumbar plexus which resides in the psoas muscle.(Figure 5.1a & b). A 70-mm long 22-gauge or 120-mm long 20-gauge (SonoPlex Cannula) needle was advanced toward the lumbar plexus using the in-plane technique (Campoy et al. 2008; Portela et al. 2010; Vettorato et al. 2012; Portela et al. 2013; Portela et al. 2017; Tayari et al. 2017). An electrical nerve stimulator was used to confirm the proximity of the needle tip to the lumbar plexus (NMS410 Stimpod). The electrical nerve stimulator was set to a frequency of 1 Hz and a pulse duration of 0.1 ms. The electrical current was set at 2 mA and gradually decreased to 0.5 mA. When the needle tip was near the lumbar plexus, visualized with the ultrasound and the electrical nerve stimulator initiated the quadriceps motor

response after stimulating the femoral nerve, the study solution (ropivacaine or sterile 0.9% saline) was injected around the plexus. (Figure 5.1a & b). The needle was repositioned under ultrasound guidance until the local anesthetic or sterile 0.9% saline reached all nerves within the plexus.

5.2.1.2 Sciatic nerve regional analgesia

The present study applied the ultrasound guidance technique following Echeverry et al. (2010). The transducer probe was placed immediately distal to the greater trochanter of the femur and ischiatic tuberosity. The image of the nerve was in the cross-sectional axis view. The needle was inserted from the posterior part of the thigh and in-plane to the ultrasound beam (Figure. 5.1c). The needle was advanced until the tip was close to the sciatic nerve, and the electrical nerve stimulator (0.5 mA, frequency 1 Hz, and pulse duration 0.1 ms) elicited stifle joint flexion due to the contraction of the gastrocnemius muscle. The calculated volume of ropivacaine or sterile 0.9% saline was injected to surround the sciatic nerve (Figure. 5.1d). The needle was repositioned as needed to allow the study solution to spread appropriately.

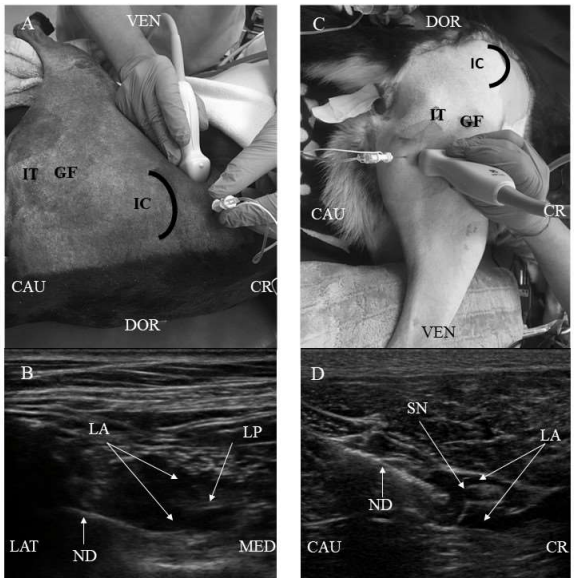

Figure 5.1 Ultrasound (US) transducer, needle position, and ultrasonography image of the lumbar plexus and sciatic nerve blocks. (a) Transducer probe was placed cranial to the iliac crest (IC) and directly perpendicular to the long axis of the dog's body to perform lumbar plexus block; (b) US image of the lumbar plexus (LP) that was encircled by ropivacaine (LA); (c) transducer probe was placed distal to the line between the ischiatic tuberosity (IT) and greater trochanter of the femur (GF) to perform sciatic nerve block; (d) US image of the sciatic nerve (SN), which was encircled by ropivacaine (LA). CR, cranial; CAU, caudal; DOR, dorsal; LAT, lateral; MED, medial; VEN, ventral; ND, insulated need

5.2.1.3 Regional analgesia technique assessment

The person who conducted the nerve blocks recorded the difficulty and duration of performing the blocks. The difficulty score was recorded following the feasibility of performing the blocks. The score ranged from 1 to 5. A score of 1 indicated an easy, quick technique. A score of 5 indicated a difficult technique. The difficulty depended on the ability to identify the nerves under ultrasound. Visualization of the nerve and the distance from skin to the nerves were affected by the dogs' body condition, body size, and muscle mass. Obese and large dogs required a deeper acoustic window, which decreased the resolution and increased the difficulty of visualizing the target nerve. Muscle atrophy also reduces the ability to visualize target nerves due to altering structures and visualization. The time required to perform the blocks was recorded from when the ultrasound transducer probe was placed on the skin until both blocks were performed.

5.2.1.4 Test Solution

The local anesthesia used in the study was ropivacaine. The drug was chosen because of its benefits of 9-11 hours of analgesic effect and lesser cardiotoxicity than bupivacaine (Campoy et al. 2012a; Tayari et al. 2017). Other adjuvant drugs were not used in this study to decrease study variables. Epinephrine may not prolong the ropivacaine duration of action, as reported with other local anesthesia drugs (Hurley et al. 1991; Garcia 2015). Dexmedetomidine was not selected because it adds variables in onset and duration (Trein et al. 2017). In an ultrasound-guided lumbar plexus block study performed by Echeverry et al. (2012), used a lower volume of ropivacaine (0.2 mL/kg), resulting in an adequate nerve block. In another study using ropivacaine at 0.1 mL/kg for an ultrasound-guided lumbar plexus block, the analgesic effect was 90%, indicating the drug's inadequate distribution (Tayari et al. 2017). To provide sufficient analgesia and decrease the chances of developing toxicity, 0.5% ropivacaine at 0.15 mL/kg for each block was used for the lumbar plexus and sciatic nerve blocks.

5.2.2 Anesthesia management

Food, but not water, was withheld for 12 hours before anesthesia in dogs in both the RA and CON groups following hospital protocol. All dogs were administered hydromorphone (0.2 mg/kg) and atropine

sulfate (0.02 mg/kg) subcutaneously 30 minutes before anesthesia induction for premedication. Hydromorphone was chosen to provide sedation and pre-emptive analgesia effects. In a pilot study, a lower dose of hydromorphone (0.1 mg/kg) was administered, and the dog woke up when the painful limb was manipulated during radiology. Therefore, this study increased the hydromorphone dose to 0.2 mg/kg. Atropine was administered to resolve the bradycardia effect that results from hydromorphone. A catheter (20 gauge) was aseptically placed in a cephalic vein, and a fluid bolus of lactated Ringer's solution (LRS; 10 mL/kg) was administered over 5 to 10 minutes before anesthesia induction. A fluid bolus was given before induction to decrease the chance of developing hypotension during propofol administration. LRS (5 mL/kg/hour) was infused continuously during anesthesia. The fluid rate was used to correct ongoing fluid loss and support cardiovascular function. This rate is recommended by AAHA guidelines (Davis et al. 2013). Propofol (PropoFlo; Abbott Laboratories Inc., IL, USA) was titrated intravenously (IV) to induce anesthesia until the patient was in a condition to place the endotracheal tube. Isoflurane (Akorn, IL, USA) in oxygen was administered via an endotracheal tube connected to a circle rebreathing system and anesthetic machine to maintain general anesthesia. The initial anesthesia vaporizer setting was 2%, and the oxygen flow was set at 1 L/minute. A three-liter rebreathing bag was used with all dogs because this reservoir bag size was sufficient for all dogs (Hughes 2016).

To monitor patient vital parameters, continuous electrocardiography (ECG), pulse oximetry, respiratory rate, oscillometric and invasive blood pressure (dorsal pedal artery), side stream capnography (End-tidal carbon dioxide: $EtCO_2$), and esophageal temperature were monitored throughout anesthesia using a multiparameter monitor (VetTrends V). A direct blood pressure transducer (Argotrans) was zeroed to atmospheric pressure and placed at the right atrium level using the sternum in lateral recumbency or the jugular fossa in dorsal recumbency as a guideline. Anesthesia monitored data were recorded every 5 minutes during the study. An active warming device (3M Bair Hugger model 505) was used to maintain the dog's body temperature; if the temperature reached 100°F, the device was turned off. The temperature was maintained to prevent a change in isoflurane requirement and complications, including anesthetic overdose, bradycardia, cardiac arrhythmia, delayed wound healing and infection, coagulation and metabolic

changes, and delayed recovery from anesthesia (Satas et al. 1996; Oncken et al. 2001; Pottie et al. 2007; Grimm 2015).

After being properly monitored, the anesthetized dogs were taken to the radiology service to perform stifle radiographs for TPLO surgery planning. Once dogs returned to the anesthesia preparation room, ultrasound-guided regional analgesia or nerve blocks were performed with the assigned study solution (ropivacaine or sterile 0.9% saline). A board-certified anesthesiologist performed the ultrasound-guided lumbar plexus and sciatic nerve blocks.

5.2.2.1 Study design for data acquisition

When ultrasound-guided lumbar plexus and sciatic nerve injections were accomplished, the isoflurane vaporizer was set at 1.25% for all patients. The isoflurane was set at 1 MAC in anticipation for dogs to mildly respond to surgical stimulation. Studies have shown that surgical stimulation often requires 1.2-1.3 MAC without premedication (Barletta et al. 2016). After 10 minutes and without stimulation and with the isoflurane vaporizer setting at 1.25%, baseline vital parameter data were collected for the study. Heart rate (HR), mean arterial blood pressure (MAP), and respiratory rate (RR) were obtained and averaged (three to five readings over 10 minutes)

Dogs breathed spontaneously to simulate common veterinary anesthesia practice. However, if the $EtCO_2$ was greater than 55 mmHg (7.33 kPa), the dog would receive intermittent positive pressure ventilation manually to prevent further increase. An $EtCO_2$ higher than the target value may reduce the requirement of inhalation anesthesia by increasing the pain threshold that may confound the isoflurane requirement (Grönroos & Pertovaara 1994; Wu et al. 2021).

When anesthesia and analgesia were considered insufficient during surgery. Rescue analgesia was administered when a dog responded to surgical stimulation with purposeful movement or when HR, MAP, or RR increased 20% above baseline. Fentanyl (2 µg/kg) was administered intravenously. If three fentanyl rescue analgesia doses were administered consecutively within 5 minutes and the anesthesia plane remained inadequate (HR, MAP, or RR did not return within 20% or the patient continued with purposeful movements), the isoflurane vaporizer setting was increased by 0.25%. When the isoflurane vaporizer setting

was changed, whether increasing or decreasing, the reservoir bag was manually emptied, and the oxygen flow rate was increased to 2 L/minute for 10 minutes. Then, the oxygen flow rate was decreased to 1 L/minute. The emptying bag and increased oxygen flow procedures were performed to shorten the time for isoflurane in the anesthesia machine system to reach the desired setting earlier than just changing the vaporizer setting. Every change in the vaporizer setting and the amount of rescue fentanyl administered were recorded for analysis.

Dogs were considered deeply anesthetized when they developed hypotension with MAP <60 mmHg. To decrease the anesthesia plane and manage this complication, a stepwise protocol following the 2013 AAHA/AAFP guidelines was followed (Davis et al. 2013). First, the isoflurane vaporizer setting was decreased by 0.25%. If no improvement in MAP was observed within 5 minutes, an LRS bolus of 10 mL/kg IV was administered over 5 minutes. If MAP did not improve with the LRS bolus, a hetastarch bolus of 5 mL/kg IV was administered over 5 minutes. If MAP remained below 60 mmHg, a dopamine infusion (5 mcg/kg/minute) was adjusted until MAP increased >60 mmHg. If the dog had a HR less than 20% from baseline, atropine (0.02 mg/kg) was administered into the triceps muscle. Data was recorded for analysis.

5.2.3 Postoperative study design and data acquisition

After surgery, postoperative radiography was obtained to confirm the correct TPLO plate and screw placement. At this time, all dogs received carprofen (2.2 mg/kg) and hydromorphone (0.1 mg/kg) subcutaneously to control postoperative pain. Dogs recovered in the intermediate care ward (ICW), and the urinary bladder was expressed to provide comfort. Two hours after extubation, the dogs were walked outside to assess pain and the ability to use their leg. After the walk, all dogs received physical therapy for 30 minutes, including cold compression, range of motion movement, transcutaneous electrical nerve stimulation, and laser therapy. Physical therapy was performed to build muscle mass and strength, prevent muscle atrophy, increase the range of motion while the stifle was flexed or extended, improve the ability of the affected limb to bear weight faster, and promote wound healing (Monk et al. 2006; Gagnon et al. 2016; Barnes et al. 2019).

An investigator unaware of the dog group allocation assessed recovery quality and pain during the postoperative period. Recovery quality at extubation was assessed using a previously published score (Becker et al. 2013) (Table 5.1). Dexmedetomidine (1 μg/kg.) was administered intravenously when the recovery score was 2 or greater. The drug was readministered if needed until the dog settled and the recovery score was less than 2. Dexmedetomidine is an alpha-2 agonist that provides analgesia, sedation and decreases anxiety. A high recovery score can result from dysphoria/emergence delirium or pain, which is difficult to differentiate. Dexmedetomidine was used to treat both causes of poor recovery quality.

Table 5.1 Recovery score (modified from Becker et al. (2013) study)

Score	Dog's expression description
1	Calm
2	Transiently whining or gently paddling
3	Whining or paddling with uncoordinated movement, sensitive to noise, and getting worse over time
4	Agitation by trying to bite or thrashing their body in an uncoordinated manner

Dogs were assessed for pain using 3 different assessment tools. A modified version of the University of Melbourne Pain Scale (MUMPS), Colorado State University Acute Canine Pain Scale (CSUPS), and visual analog pain scale (VAS). The University of Melbourne Pain Scale is an assessment that evaluates the patient by using multiple descriptions of behavior related to pain. This system is a reliable pain assessment system, but it may not detect subtle behavioral changes or consider the effect of post-anesthesia sedation (Saberi Afshar et al. 2017). Modification of the MUMPS scale was based on a previous study showing that heart rate, respiratory rate, and pupil size were not always biologically related to the patient's pain. Thus, these physiological parameters were removed from the assessment (Holton et al. 1998) (Table 5.2). The CSUPS is a composite of acute pain using observation and hands-on assessments to evaluate the psychological signs, behavioral signs, and palpation response (Figure 5.2). The assessment begins with quiet observation of the patient from a distance. Then the patient is assessed for reaction to gentle palpation of the wound and whole body. Responses include muscle tension, heat, and reaction to palpation. The CSUPS is the most straightforward pain scale. It has a specific description of each behavior to reduce inter-observational variability and is commonly used at CSU. The CSUPS was used in this study

despite not being scientifically validated (McKune et al. 2015). The visual analog pain scale (VAS) is a subjective simple continuous scale consisting of a 100 mm horizontal line with a vertical line border of both ends and divisions every 10 mm (1 cm). The point at 0 mm at the left border refers to no pain, and the point at 100 mm on the right border represents the worst pain imaginable (Figure 5.3). The evaluator marks the line at a distance that correlates to the pain. The VAS test is simple, can be evaluated over time, and can be used for recording the response to analgesic treatment. The score is also sensitive, and the patient can be treated promptly if pain is in doubt. However, it has significant observer variability, limiting its use in a multiple observer study. The observer must be trained in its use before the evaluation. The pain score cannot be objectively quantified; that is, a score of six does not always refer to twice the pain of a score of three. This complicates comparing the severity of pain and response to analgesia among patients (McKune et al. 2015). Three pain scale systems were used in the study because no universal or self-sufficient pain assessment system currently exists (Saberi Afshar et al. 2017). MUMPS benefits from well-described behavior changes that represent pain. However, subtle changes may not be recognized. The VAS score is sensitive to detecting subtle changes. Nonetheless, the high inter-observer variability is an important limitation. The CSUPS has a low inter-observer variability because it requires minimal interpretation. The CSUPS is commonly used in our institution, and familiarity with the pain scale can increase the reliability and consistency in making analgesia treatment decisions. The disadvantage of CSUPS is it lacks validation from clinical studies.

Table 5.2 Modified University of Melbourne Pain scale

Posture		Score
	Comfortable, moving freely around and on the surgical site	0
	Guarding or protecting the affected surgical area	2
Mental status (Choose only one)		
	Awake, normal, and calm	0
	Sleeping	0
	Partial rough recovery (Paddling and vocalization)	1
	Rough recovery (vocalization, thrashing, and paddling)	2
Response to palpation (choose only one)		
	Allows palpation of surgical site	0
	Allows but then moves away, tenses, or looks when the area is touched	1
	Increased painful expression when the area is touched	2
	Extremely painful when touching	3

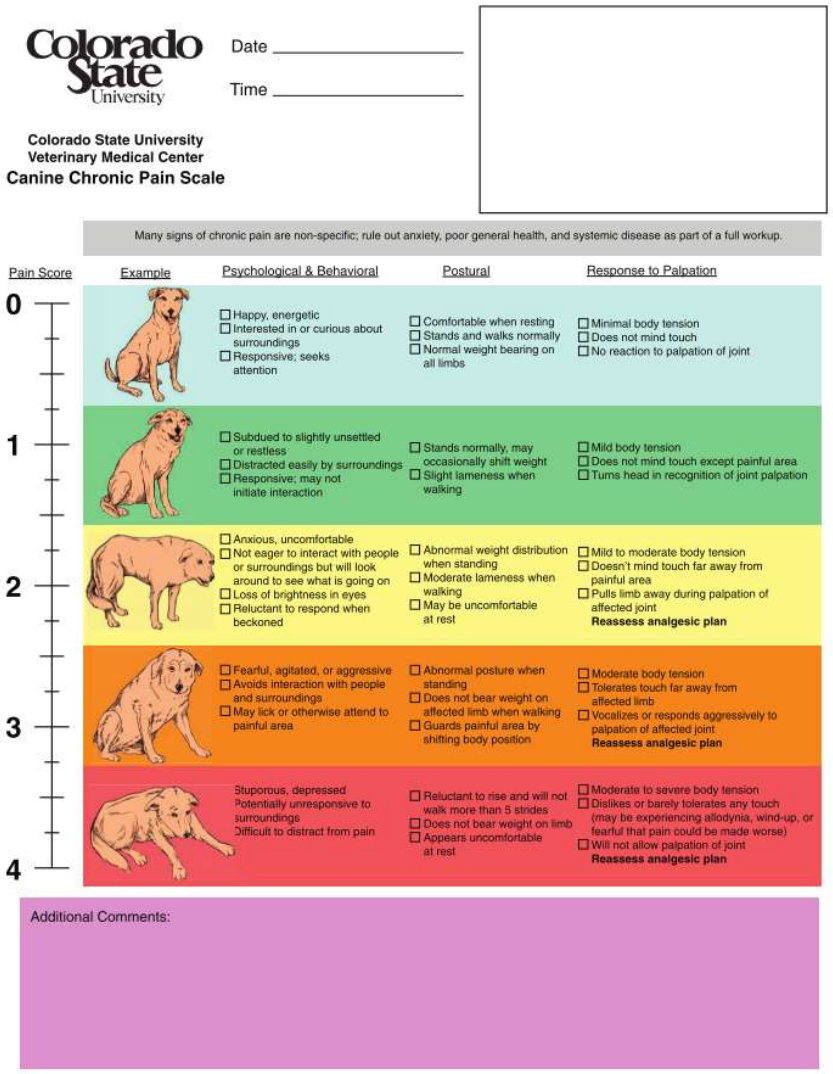

Figure 5.2 Colorado State University Acute Pain scale

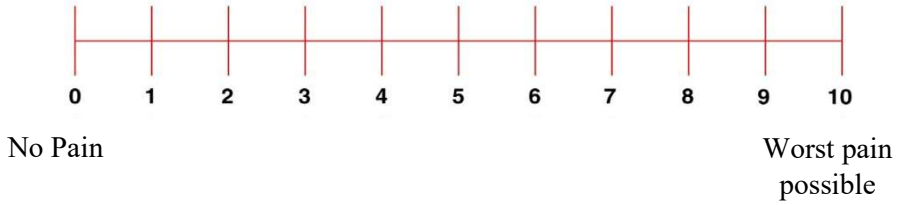

Figure 5.3 Visual analog pain scale

Pain was assessed in all dogs before premedication to establish baseline values and ensure all dogs were pain free. Pain was assessed after extubation and 2 hours after extubation. Pain was assessed using only the CSUPS 6 and 12 hours after extubation. The CSUPS was used at 6 and 12 hours because ICW staff are familiar with this scale system, leading to consistent pain evaluation results and the decision for rescue analgesia administration. Postoperative rescue analgesia was administered if the MUMPS score was equivalent to or greater than 2, the CSUPS score was equivalent to or greater than 1, or the VAS score was greater than 2. These thresholds were used to ensure that every patient was comfortable and not suffering from postoperative pain.

Postoperative rescue analgesia consisted of a continuous-rate infusion of fentanyl (2 mcg/kg/hour). If pain was not well controlled, fentanyl boluses (2 mcg/kg) were administered intravenously until pain scores were below the threshold. In cases where fentanyl was ineffective in controlling postoperative pain or if a dog showed signs of fentanyl side effects, either SC methadone (0.2 mg/kg) or IV dexmedetomidine (1 mcg/kg) was administered. If a dog was restless and considered anxious but with a low pain score (e.g., barking, howling, or pawing at the kennel door), either dexmedetomidine (1 µg/kg) or acepromazine (0.01 mg/kg) was administered intravenously until the dog calmed down.

5.2.4 Statistical analysis

To compare the RA and CON groups, GraphPad Prism 6.07 was used (GraphPad Software, CA, USA). The Shapiro-Wilk test was used to determine normality distribution followed by selecting the appropriate statistical tests. Continuous variables with normal distribution were compared using a two-tailed Student's t-test. Normally distributed data include anesthesia and surgery durations and intraoperative fentanyl. Continuous variables and non-normally distributed data were tested using the Mann-Whitney test

to compare rank differences. These data consisted of age, body weight, propofol, and recovery score. Normally distributed continuous variables that involved repeated measures were tested by repeated-measures analysis of variance followed by the Bonferroni correction to compare HR, MAP, RR, postoperative fentanyl, and pain scales among time within each group. These tests were used because the data within each group was normally distributed, and the dog was counted as the repeated variable. For non-normally distributed continuous variables that required repeated measures, the Friedman test with Dunn's multiple comparison tests was used to compare HR, MAP, RR, postoperative fentanyl, and pain scales among time between groups. These tests were used because the overall data from both groups were not normally distributed; therefore, a non-parametric repeated test was used. Categorical variables were compared between groups using Fisher's Exact Test (sex, hypotension incidence) because the number of incidences in each group was less than five. Pearson's correlation coefficient was used to determine the correlation between the amount of intraoperative rescue analgesia (fentanyl) and recovery quality. The time to receive drugs in the postoperative period was determined using Kaplan-Meier and log-rank tests for survival analysis. A p-value of <0.05 was considered to indicate statistical significance. Normally distributed data are presented as the mean ± standard deviation (SD), and non-normally distributed data are presented as the median (range). Numbers were shown in both types to indicate the distribution of the data. Mean is the average of the data set, and it is appropriated for the group of data that are not distorted to the high or low discrepant value. The Median is the middle value in the distribution in ascending order. The median is not affected by the discrepant value. Therefore, the median can represent non-normal distribution data (Rodrigues et al. 2017).

5.3 Results

The results of the study are presented here and include a description of patient signalment to indicate the character of the dogs enrolled in the study.,

5.3.1. Group signalments

Twenty dogs were enrolled in the study, with 10 dogs assigned to the RA group and 10 dogs assigned to the CON group. The RA and CON groups both included 5 mixed breed dogs and 5 purebred dogs. (Table 5.3).

Table 5.3 Breed distribution of the enrolled dogs who underwent general anesthesia received lumbar plexus and sciatic nerve blocks using 0.5% ropivacaine (RA) and sterile 0.9% saline (CON) (n = 10 per group).

Breed	Number in RA group	Number in CON group
Mixed-breed	5	5
Labrador Retrievers	2	2
Golden Retrievers	1	
Australian Heeler	1	
German Shepherd	1	
Australian Shepherd		1
Staffordshire Terrier		1
Weimaraner		1

The dogs in the RA and CON groups were aged [median (range)] 6 (3-9) and 6 (2-7) years, weight 34 ± 4.5 kg and 33.2 ± 7.2 kg and consisted of 6 females and 4 males and 5 females and 5 males, respectively. There was no significant difference between the groups regarding age (p = 0.7), body weight (p = 0.7) or sex (p = 1).

5.3.2. Anesthesia Characteristics

This study recorded the time from anesthesia induction until the endotracheal tube was extubated. The important events duration included the anesthesia duration and the extubation time. The anesthesia duration was recorded from the induction time to turning the gas off. The extubation time is between turning off the isoflurane vaporizer to when the airway was adequately protected by vigorously swallowing (Grubb et al. 2020), and the endotracheal tube was removed from the dog.

The anesthesia durations in the RA and CON groups were 178.5 ± 10.0 and 167.0 ± 6.4 minutes, respectively. There was no difference in anesthesia duration between the groups (p = 0.4). Anesthesia duration was divided into five duration segments, including induction to the nerve block duration, nerve block duration, nerve block to start of surgery duration, surgical duration, and end of surgery to turning the

isoflurane off duration. The time was divided in this fashion because each duration had a particular incidence described in table 5.4. The duration of the events are shown in Table 5.5

Table 5.4 The events description details during the anesthesia

Event	Description
Induction to nerve block duration	Time from anesthesia induction until before the nerve block started. This duration was for patient instrumentation, surgical site preparation, and preoperative radiography.
Nerve block duration	Time started when the ultrasound probe was placed on the dog until the local anesthetic was injected.
Nerve block to surgery duration	The time from the end of the nerve block until surgery began. This duration was used for the baseline values of heart rate, respiratory rate, blood pressure, and drug requirement in the study.
Surgical duration	Time from when the incision was made at the skin until the last suture was placed.
End of surgery to turning the isoflurane off	Time from the end of surgery until the isoflurane vaporizer was turned off. During this time, the dog was taken for postoperative radiographs and prepared for admittance to the intermediate care ward.

Table 5.5 Anesthesia duration details and extubation time of dogs undergoing general anesthesia and receiving lumbar plexus and sciatic nerve blocks using 0.5% ropivacaine (RA) and sterile 0.9% saline (CON) (n = 10 per group).

Duration	RA (minutes)	CON (minutes)	p-value
Induction to nerve block duration	50 (25-54)	47 (25-62)	0.4
Nerve block duration	4.5 ± 0.9	4.4 ±1.2	0.9
Nerve block to surgery duration	29 ± 14	28.6 ± 8.3	0.9
Surgical duration	73.1 ± 14.7	70.7 ± 12.0	0.7
End of surgery to turn the gas off duration	25.3 ± 4.8	21.9 ± 4	0.1
Extubation time	28.5 ± 16.1	26.8 ± 12.8	0.8

5.3.3 Surgery Duration Characteristics

Surgical duration was divided into 4 events based on stimulation that the dogs received intraoperatively. Each event is a different stimulation that may have affected the requirement of anesthesia and analgesia drugs during the time frame. A description of the surgical events is provided in Table 5.6, and the duration of the events are shown in Table 5.7.

Table 5.6 The events description details during the surgery

Event	Description
Skin incision	Time from the first skin incision until the arthrotomy started
Arthrotomy	Time from when the arthrotomy started to before the osteotomy started.
Osteotomy	Time from when the osteotomy started until the before the skin was closed.
Skin closure	Time from when the first stitch of the skin was placed until the end of skin suturing.

Table 5.7 Surgical duration details of dogs undergoing general anesthesia and receiving lumbar plexus and sciatic nerve blocks using 0.5% ropivacaine (RA) and sterile 0.9% saline (CON) (n = 10 per group).

Duration	RA (minutes)	CON (minutes)	p-value
Skin incision	5.5 ± 2.2	6.4 ± 1.7	0.3
Arthrotomy	17.1 ± 6.3	13 ± 4.3	0.1
Osteotomy	41.1 ± 8.5	42.5 ± 10.5	0.7
Skin closure	8.6 ± 2.7	7.4 ± 2.3	0.3

5.3.4. Intraoperative Anesthesia and Analgesia Requirements

Anesthesia was induced by propofol titration until the endotracheal tube was placed. The amount of propofol used was not different between groups. For the RA group, the dose was 4.4 ± 1.5 mg/ kg, and the dose for the CON group was 4.6 ± 1.3 mg/kg (p = 0.7). While performing the ultrasound-guided lumbar plexus and sciatic nerve blocks with ropivacaine (RA group) and sterile normal saline (CON group), the difficulty score was calculated; for both groups, the average score was 1.6 ± 0.7 (RA =1.6±0.8, CON = 1.6±0.7, p = 0.99). The difficulty score correlated with the nerve block duration (R^2= 0.33, p = 0.037), indicating that extra time was needed for managing a difficult nerve block case. Under anesthesia, isoflurane was used for maintenance. When dogs were moving, or vital parameters changed (heart rate, respiratory rate, or blood pressure parameters increased to greater than 20% of the baseline), fentanyl rescue analgesia was administered. A repeated dose of fentanyl was administered until the vital signs were within 20% of the baseline and prevented the dogs' movement. If vital signs did not decrease after three repeated doses of fentanyl within 5 minutes, isoflurane was increased by 0.25% to maintain the depth of anesthesia. In the RA group, the cumulative fentanyl rescue analgesia administered during surgery was 14 ± 9 μg/kg and 25 ± 10 μg/kg for the CON group (Figure. 5.3; p = 0.02). During surgery, within each surgery event, the dose

of rescue fentanyl analgesia requirements between RA and CON groups were not different. However, the number of dogs in the CON group that required rescue fentanyl analgesia tended to be greater than the RA group in almost every surgical event except at skin closure (Figure 5.4).

Similarly, the average isoflurane vaporizer settings used during surgery were 1.5 ± 0.07 and 1.8 ± 0.09% for the RA and CON groups, respectively (p = 0.03). However, within each surgery event, the isoflurane vaporizer settings between RA and CON groups were not different (Figure 5.5).

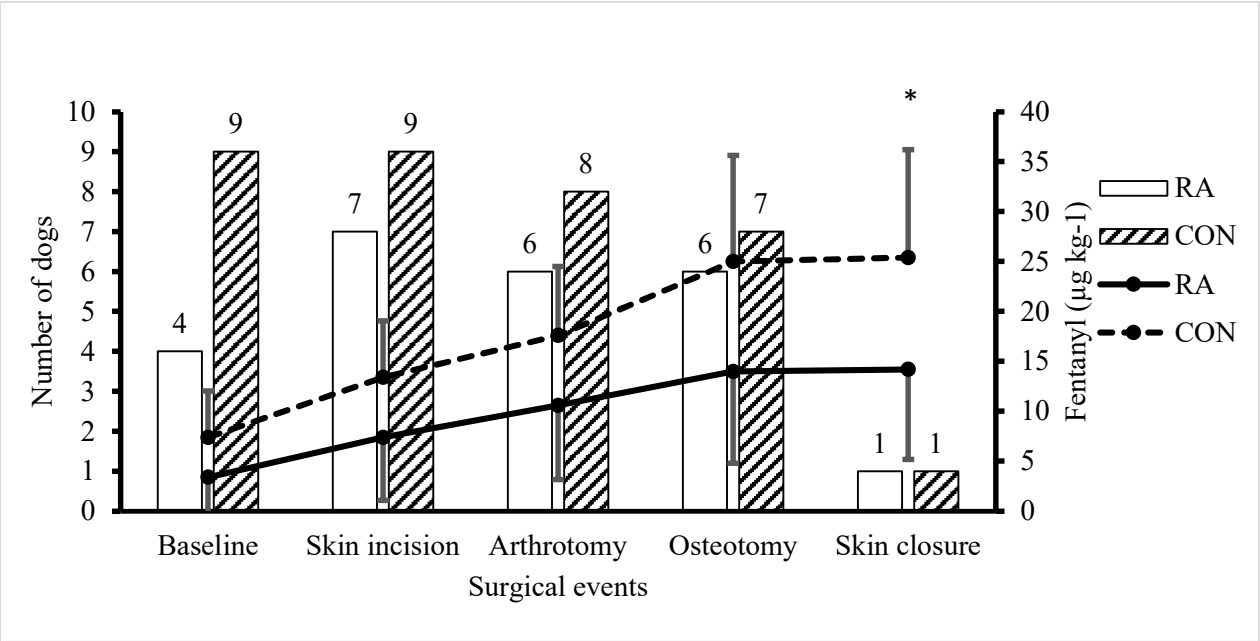

Figure 5.4 Intraoperative fentanyl rescue analgesia at each surgical event. The column represents the number of dogs administered rescue fentanyl analgesia for each event (numbers shown over each bar), and the lines represent the cumulative fentanyl dose required for the procedure. All dogs were under isoflurane anesthesia and received lumbar plexus and sciatic nerve blocks with ropivacaine (RA) or sterile 0.9% saline (CON) when undergoing tibial plateau leveling osteotomy surgery (n = 10 per group). Data are shown as the mean ± standard deviation. * Significant difference between groups (p = 0.02)*

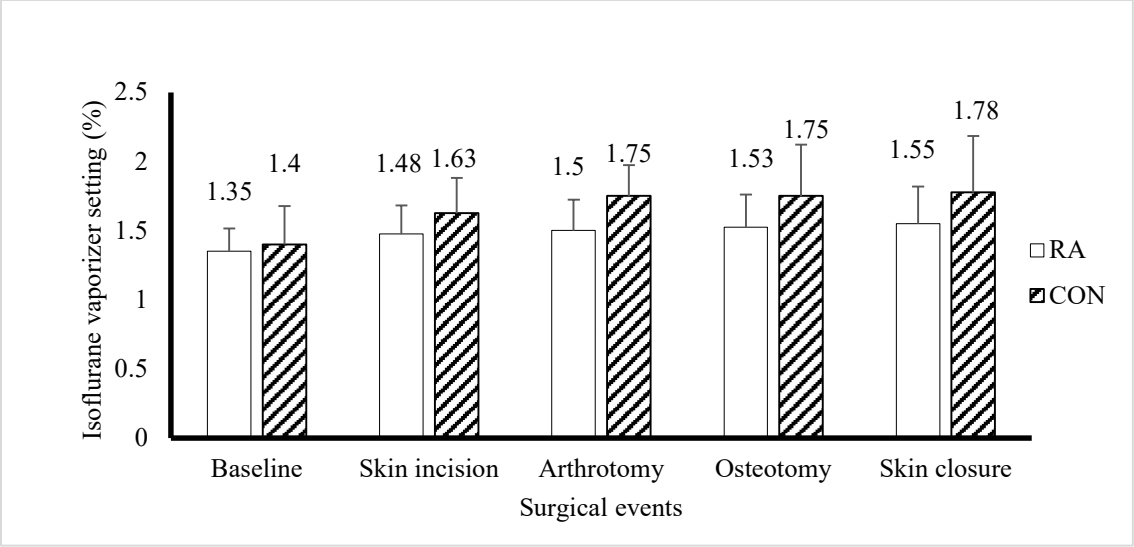

Figure 5.5 Intraoperative isoflurane vaporizer settings at each surgical event during the procedure. The column represents the isoflurane vaporizer setting (%) for each event (numbers show over each bar). All dogs were under isoflurane anesthesia and received lumbar plexus and sciatic nerve blocks with ropivacaine (RA) or sterile 0.9% saline (CON) when undergoing tibial plateau leveling osteotomy surgery (n = 10 per group). Data are shown as the mean ± standard deviation.

5.3.5. Physiologic parameters under anesthesia

Overall respiratory rate, heart rate, and mean arterial blood pressures before and during surgery are shown in table 5.8.

Table 5.8 Intraoperative physiologic parameters values by the surgical events from dogs under general anesthesia from both groups. Numbers are presented as the median (min-max)

	Surgical event				
	Baseline	Skin incision	Arthrotomy	Osteotomy	Skin closure
Respiratory rate (breaths/minute)	13 (6-26)	13 (2-27)	11 (2-27)	9 (3-26)	9 (3-28)
Heart rate (beats/minute)	91 (69-141)	92 (71-146)	86 (66-144)	95 (72-128)	93 (70-119)
Mean arterial blood pressure (mmHg)	71 (64-108)	79 (58-128)	77 (67-95)	74 (52-99)	76 (64-102)

Physiologic parameters were not different within each group or between RA and CON groups. Before surgery and during surgery, physiologic parameters were not significantly different (p >0.1). The

absence of difference over time and between groups was expected as the study methodology aim was to maintain all vital parameters within 20% from baseline, obtained before surgery.

On the other hand, hypotension was a common complication observed during anesthesia. From the 20 dogs studied, 12 dogs became hypotensive with MAP of 54 (52-58) mmHg during surgery. The number of dogs developing hypotension was not different between-group ($p = 0.16$). The RA group had four dogs become hypotensive with a mean arterial blood pressure average of 55 (52-58) mmHg. The CON group had eight dogs that developed hypotension with a mean arterial blood pressure average of 54 (52-58) mmHg. In the RA group, dogs that develop hypotension required fewer steps to treat this complication than in the CON group. Three out of four hypotensive dogs in the RA group required only a decrease in the isoflurane vaporizer setting and a 10 mL/kg crystalloid fluid bolus to improve blood pressure and increase MAP above 60 mmHg. The remainder hypotensive dog from the RA group required an additional 5 mL/kg of colloid to improve MAP above 60 mmHg. In contrast, six of eight dogs in the CON group required further treatment to improve blood pressure and increase MAP above 60 mmHg. The six hypotensive dogs from the CON group required a decrease in isoflurane vaporizer setting, a crystalloid fluid bolus of 10 mL/kg, a colloid fluid bolus of 5 mL/kg, and continuous infusion of dopamine administration to bring the MAP above 60 mmHg. The two additional hypotensive dogs from the CON group responded to treatment with a decreased isoflurane vaporizer setting and 10 mL/kg crystalloid fluid bolus. Hypotension treatment with dopamine did not elicit any cardiac arrhythmias. A summary showing the incidence of hypotension and the treatment required to solve this complication is shown in Table 5.9.

Table 5.9 Treatment response for hypotension during anesthesia in dogs that received lumbar plexus and sciatic nerve blocks with ropivacaine (RA group, 4 out of 10 dogs developed hypotension) or sterile 0.9% saline (CON group, 8 out of 10 dogs developed hypotension) and underwent tibial plateau leveling osteotomy

Treatment	Group	
	RA	CON
Crystalloid bolus	3/4	2/8
Crystalloid bolus + colloid bolus	1/4	0/8
Crystalloid bolus + colloid bolus + Dopamine	0/4	6/8

A second anesthesia complication observed in dogs from both groups was hypercapnia, which occurred when the $EtCO_2$ was greater than 45 mmHg. Hypercapnia or hypoventilation was observed in all patients intraoperatively. During anesthesia, all dogs developed hypercapnia to the point that $EtCO_2$ was greater than 55 mmHg, which was the trigger point to initiate intermittent positive pressure ventilation. Assisted intermittent positive pressure ventilation was performed manually until the $EtCO_2$ was lower than 45 mmHg. Seven of ten dogs in both the RA and CON groups had $EtCO_2$ restored to less than 45 mmHg and were returned to breathing spontaneously. No other complications were observed in any of the dogs during the study.

5.3.6. Recovery from anesthesia and surgery

At the end of anesthesia, dogs from both groups were recovered and extubated in the same room with the same personnel (VTH-intermediate care unit). The urinary bladder was expressed before extubation to prevent discomfort, and the IV catheter was secured to prevent dislodgement. The recovery quality for each dog was scored at extubation using the recovery quality assessment system previously described in this chapter Materials and Methods section. A difference in recovery scores was observed between groups ($p = 0.04$; Table 5.10). Recovery scores were better (lower) in the RA group, with dogs showing the soft and subtle sound of whining and gentle paddle at extubation then settling down. Only one dog in the RA group had a poor recovery score showing agitation, thrashing in an uncoordinated manner, with intermittent crying. In contrast, five dogs in the CON group had poor recovery scores with agitated recoveries, extreme paddle with uncoordinated movement, and loudly crying that gentle handling could not control. Dogs with high or poor recovery scores (any score above 2) were treated with dexmedetomidine 1 µg/kg IV. The six dogs with poor recovery scores were treated with one dose of dexmedetomidine. Two dogs in the CON group required a second dose of dexmedetomidine.

Poor recovery from anesthesia can be associated with dysphoria/emergence delirium, pain, anxiety, or bladder distension (Lester et al. 2003; Hofmeister et al. 2006; Jiménez et al. 2012; Becker et al. 2013; Lloyd 2017; Kropf & Hughes 2019). In previous studies, dysphoria/emergence delirium involved opioids and inhaled anesthetics (Hofmeister et al. 2006; Keating et al. 2013; Kanaya et al. 2014; Kropf & Hughes

2019). The correlation between poor recovery and fentanyl administration or inhaled anesthetic vaporizer setting was explored. There was no correlation of the total amount of intraoperative fentanyl and the recovery score (R^2 =0.09, p = 0.18). The time from the last fentanyl administration may also affect the recovery score. The administration of fentanyl may be sufficient to cause poor recovery quality if the time between the last fentanyl administration and extubation is short, and vice versa. However, the correlation between the extubation time and recovery score was weak (R^2 =0.46, p = 0.009). Based on these results, the time between the last fentanyl dose and extubation did not correlate with the recovery quality. Another drug that can affect recovery quality is inhaled anesthesia (Picard et al. 2000; Chandler et al. 2013). Results showed that isoflurane vaporizer settings and recovery quality were not correlated (R^2 =0.06, p= 0.28). There is a chance that isoflurane may not get sufficiently eliminated and may cause poor recovery if the time between turning the vaporizer off to extubation is short. In the present study, extubation time did not correlate with the recovery score (R^2 =0.14, p = 0.1). As a result, isoflurane concentration and duration from turning the gas off to extubation did not correlate to recovery quality.

Only one complication was observed during the recovery. One dog in the CON group recovered with excitement, thrashing, and continuous howling. The recovery was rough, to the point that the bandage and the catheter were dislodged, which resulted in the need to replace the IV catheter and incisional rebandage. After receiving dexmedetomidine as rescue sedation, the dog relaxed for 30 minutes, and acepromazine was needed repeatedly to calm the patient down.

5.3.7. Postoperative pain and behavior assessment and management

Pain is important during the postoperative period because it can lead to an uncomfortable recovery and predispose to chronic pain. Thereby, pain was assessed in all dogs. Pain was first assessed before premedication to establish a baseline value. Pain was assessed again during the recovery period starting at extubation from anesthesia and 2, 6, and 12 hours after extubation. Pain was assessed by investigators unaware of the dog's treatment group using the CSUPS, MUMPS, and VAS scoring systems. As mentioned previously in this chapter, each scoring system has its advantages and disadvantages (Saberi Afshar et al.

2017). In addition, other behaviors that indicated signs of discomfort, such as agitation, howling, or restlessness, were assessed by the same investigator and intermediate care unit staff.

Pain score results are shown in Table 5.10. The scores were not different between groups or over time. This is expected because the study methodology aimed to provide dogs with comfortable recoveries during the postoperative period. Postoperative comfort was achieved by setting the threshold to treat pain or discomfort to be quite low; MUMPS greater than 2, VAS greater than 2, and CSUPS greater than 1 triggered rescue analgesia. Once the pain score was greater than the threshold of any pain score system, fentanyl was used as rescue analgesia. The time for the first rescue postoperative analgesia administration was recorded. The Kaplan-Meier survival analysis curve (Figure 5.6) showed when dogs received their first rescue analgesia. The median time for the first postoperative rescue analgesia was 10.5 hours for the RA group and 0.5 hours for the CON group ($p = 0.04$). This indicated that dogs in the RA group had a prolonged analgesic effect and required rescue analgesia later than dogs in the CON group. The number of dogs that required rescue analgesia was five in the RA group and nine in the CON group. Of these dogs, additional fentanyl was required in three of five dogs in the RA group and four of nine dogs in the CON group to provide sufficient comfort postoperatively ($p = 0.14$). The number of dogs that required rescue analgesia within 12 hours was not statistically significant, but in the clinical aspect, the number of dogs in the CON group which was almost every patient, was significant. The sample size may not have been large enough to detect a significant difference between groups. The postoperative cumulative fentanyl requirement between the groups was not significantly different ($p = 0.15$; Figure 5.7). This may be because of in some dogs that required bolus injections in the early postoperative period and the cause of enhancing drug requirements at the early stage and required the drug just in the short period. While some patients did not require a high amount of bolus but required the rescue fentanyl for a longer periods of time, this also caused the accumulative dose to be comparable.

Table 5.10 Recovery and pain scores in 20 dogs undergoing tibial plateau leveling osteotomy surgery. Dogs received lumbar plexus and sciatic nerve blocks administered with ropivacaine (RA) or sterile 0.9% saline (CON) (n= 10 in each group). The recovery score was assessed at the time of extubation. The pain was evaluated before anesthesia, at extubation, and then at 2, 6, and 12 hours after extubation.

		Time point				
Scoring system	**Group**	**Before Anesthesia**	**Extubation**	**2 hours**	**6 hours**	**12 hours**
Recovery Score (1-4)	RA		1.4 ± 1.5*			
	CON		2.5 ± 2.2			
Modified-UMPS	RA	0	0.8 ± 0.9	0.9 ± 1.1		
	CON	0.45 ± 0.8	1.4 ± 1.7	1.7 ± 1.1		
VAS (0-10 cm)	RA	0.3 ± 0.6	0.5 ± 0.7	1.3 ± 1.3		
	CON	0.8 ± 0.8	1.7 ± 2	2.4 ± 1.6		
CSUPS (0-4)	RA	0.05 ± 0.2	0.05 ± 0.2	0.5 ± 0.6	0.4 ± 0.4	0.3 ± 0.3
	CON	0.2 ± 0.3	0.6 ± 0.8	0.9 ± 0.8	0.9 ± 0.5†	0.3 ± 0.3

Data are the mean ± standard deviation. *Significantly different from CON ($p < 0.05$). †Significantly different from the time point before anesthesia ($p < 0.05$). Modified-UMPS, Modified University of Melbourne Pain Scale; VAS, visual analog pain scale; CSUPS, Colorado State University Acute Pain Scale. The modified UMPS was removed physiologic data section from the original UMPS.

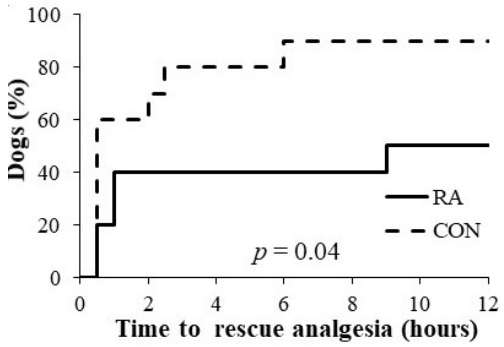

Figure 5.6 Kaplan-Meier survival analysis for dogs receiving the first dose of postoperative fentanyl rescue analgesia. All dogs recovered from anesthesia after undergoing tibial plateau leveling osteotomy surgery and received lumbar plexus and sciatic nerve blocks by ropivacaine (RA) or sterile 0.9% saline (CON) (n = 10 for each group).

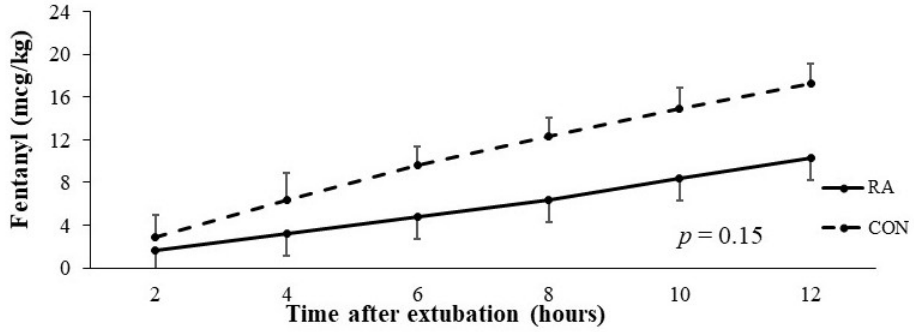

Figure 5.7 Graph of the postoperative fentanyl cumulative dose. The cumulative dose of postoperative fentanyl was administered to the dogs. All dogs recovered from anesthesia after undergoing tibial plateau leveling osteotomy surgery and received lumbar plexus and sciatic nerve blocks by ropivacaine (RA) or sterile 0.9% saline (CON) (n = 10 for each group).

During the postoperative period, one dog in the CON group received rescue fentanyl analgesia and developed signs of dysphoria. Once the dysphoria signs were detected, the rescue fentanyl was stopped. The dysphoria signs, including severe agitation and howling, decreased gradually, but pain on palpation of the wound was observed. Methadone (0.2 mg/kg) was administered via the subcutaneous route, and the dog calmed down and slept comfortably. In some dogs, dysphoria can occur with certain opioids, but not all opioids cause dysphoria to the same patient. In this case, analgesia was required, but the dysphoria was not desired; therefore, methadone was given instead of fentanyl.

In this study, dogs showing signs of agitation, restlessness, or anxiousness were observed, with the patient promptly receiving rescue sedation drugs. These rescue sedation drugs included 1 mcg/kg of dexmedetomidine or acepromazine 0.01 mg/kg intravenously. Dogs that showed extreme agitation such as thrashing, vigorous movement, or crying loud received dexmedetomidine to calm down. Dogs that showed mild signs of agitation, such as howling with slow incoordinate movement, received acepromazine. Five dogs in the RA group and seven in the CON group showed signs of agitation, restlessness, and anxiety, then received rescue sedation at the time that the signs were detected. The time to receive the first rescue sedation did not differ between groups (p = 0.5; Figure. 5.8). After administering the rescue sedation, the dogs relaxed and slept restfully.

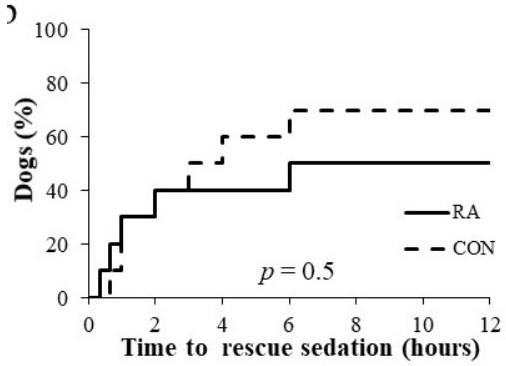

Figure 5.8 Kaplan-Meier survival analysis for dogs receiving the first dose of sedation. Survival analysis of dogs receiving the first dose of dexmedetomidine or acepromazine for sedation. All dogs recovered from anesthesia after undergoing tibial plateau leveling osteotomy surgery and received lumbar plexus and sciatic nerve blocks by ropivacaine (RA) or sterile 0.9% saline (CON) (n = 10 for each group).

5.4 Discussion

This study showed that the regional analgesia technique utilized in the study decreased the intraoperative rescue fentanyl analgesia requirements and lowered isoflurane requirement during surgery. Patients with incidence of hypotension was easily treated, had better recovery quality from anesthesia, and had a prolonged time before receiving postoperative rescue analgesia. This ultrasound-guided regional analgesia technique for the lumbar plexus and sciatic nerve enhanced intra- and postoperative analgesia and the quality of anesthesia for dogs undergoing TPLO surgery.

The results found in this study are comparable with similar studies addressing the use of ultrasound-guided peripheral anesthesia to relieve pain and improve anesthesia quality in dogs undergoing stifle surgery (Campoy et al. 2012b; Bartel et al. 2016; Palomba et al. 2020). In this study, the intraoperative analgesic requirement for dogs receiving regional analgesia with ultrasound guidance was lower than in the dogs that did not receive the block; these results were comparable to the study performed by Campoy et al. (2012a). Analgesia was effective until the postoperative period, and that pain could be controlled longer in the dogs that received regional analgesia with ultrasound guidance. These outcomes were supported by previous studies (Campoy et al. 2012b; Tayari et al. 2017)

5.4.1 Advantage of *ultrasound-guided lumbar plexus and sciatic nerve blocks*

Real-time image when using ultrasound allows detailed observation of the needle and spreading of local anesthesia. As anticipated, real-time visualization in an ultrasound-guided technique allowed the nerve block to be more precisely performed, leading to a briefer time to perform the block and requiring fewer local anesthetic drugs (Casati et al. 2007; Orebaugh et al. 2007; Koscielniak-Nielsen 2008; Lam et al. 2014). In this study, ultrasound-guided lumbar plexus and sciatic nerve blocks were performed in a short period of time for most dogs. One case offered difficulty of visualization due to patient size and not enough ultrasound wave penetration to reach deeper tissues. This difficulty was associated with the limitation of the acoustic window used in the study. The ultrasound transducer probe created an image that was only 5-6 cm deep, leading to difficulty performing a nerve block in a large dog, especially for the lumbar plexus block.

The first use of ultrasound to perform peripheral nerve blocks for patients undergoing stifle surgery was a decade ago (Campoy et al. 2012b). Previously, the block was performed only for the saphenous nerve in the inguinal area and the sciatic nerve. This technique satisfied the analgesic effect but required co-administration with heavy sedation and analgesic drugs. This incomplete analgesia effect may be because other sensory nerves that supply the stifle area are not being blocked. The additional nerves that supply the stifle joint include the obturator, genitofemoral, and lateral femoral nerves, should be blocked to provide effective analgesia. For the technique developed during this Ph.D. study, the lumbar plexus was targeted to enroll additional nerves that supply the stifle joint area. In addition, we blocked the sciatic nerve at a high level for similar reasons (Bailey & Kitchell 1987; Casati et al. 2007; Campoy et al. 2008; Portela et al. 2010; Aprea et al. 2012; Portela et al. 2013; Vettorato et al. 2013; Romano et al. 2016; Tayari et al. 2017). The technique used in this study demonstrated its efficacy by lowering the intraoperative rescue analgesia requirements. However, intraoperative fentanyl in the RA group was still required, highlighting that the RA technique did not provide complete analgesia or anesthesia of the region for surgery. It is possible that the genitofemoral and lateral cutaneous femoral nerve were not completely covered with local anesthetic because the nerves in some patients leave the iliopsoas muscle earlier to the injection area

(Echeverry et al. 2012; Monticelli et al. 2016). The volume of local anesthetic used in this study was 0.15 mL/kg per site and may not have been sufficient for blocking all the necessary nerves. Despite this, the volume of local anesthetic in this study was greater than in the previous study, which used only 0.1 mL/kg and found sufficient intraoperative analgesia for 90% of the patients (Tayari et al. 2017). Another possibility is that dogs were under low isoflurane vaporizer settings, which may not have provided sufficient anesthetic effects to other stimuli such as noise, limb movement, endotracheal tube, and instrument vibration (Campoy et al. 2008; Portela et al. 2010; Vettorato et al. 2013; Tayari et al. 2017). Therefore, the technique used in the study inferred that regional analgesia is not sufficient as the sole modality for analgesia and anesthesia during TPLO surgery in dogs. Additional analgesia techniques are required for patient comfort (Bartel et al. 2016; Trein et al. 2017).

Additional analgesia was also used during the postoperative period. Fentanyl rescue analgesia was given when any pain score reached the threshold. In this study, fentanyl rescue analgesia was required later in the RA group compared to the CON group. The mean duration of the first dose of fentanyl rescue analgesia in the RA group was 10.5 hours. The duration of rescue analgesia was comparable to a previous study (Tayari et al. 2017).

5.4.2 Complications associated with ultrasound-guided lumbar plexus and sciatic nerve blocks

In this study, the lumbar plexus and sciatic nerve block with ropivacaine showed the benefit of a better analgesic effect and provided a lower incidence of complications. Intraoperative hypotension, a common complication in this study, was found to have a lower incidence and easier to resolve in dogs in the RA group. The RA group's lower degree of intraoperative hypotension may be associated with the lower isoflurane vaporizer setting used in the RA group. Isoflurane causes drug-induced hypotension in a dose-dependent fashion (Horan et al. 1977; Steffey & Howland 1977). Isoflurane causes hypotension due to its ability to decrease stroke volume and systemic vascular resistance (Merin et al. 1991).

Hypercapnia was another intraoperative complication commonly found in our study. In general, isoflurane has a dose-dependent effect on respiratory depression (Galloway et al. 2004). The average isoflurane used in our study was less than what was used in the Galloway et al. (2004) study leading us to

believe that isoflurane was not the only cause of hypercapnia. While giving fentanyl to an awake dog does not lead to respiratory depression, it has been reported that when combined with inhalation anesthesia, the respiratory system may get depressed and lead to hypercapnia (Keating et al. 2013). In addition, the respiratory depression effect of fentanyl under inhalation anesthesia may be exacerbated when fentanyl is given consecutively. Hypoventilation from opioids is associated with its ability to abolish neuronal activity that regulates breathing and weaken the control of breathing in the brainstem (Baldo 2021).

Poor recovery from anesthesia at extubation was the most critical complication found during the postoperative period. Potential causes of poor recoveries, including emergence delirium, dysphoria, or pain. In veterinary medicine, emergence delirium refers to the uncontrolled behavior encountered when a dog rapidly regains partial consciousness after discontinuing maintenance anesthetic drugs. Dysphoria refers to recoveries with many issues, including uncontrolled pain or hypoxemia due to airway obstruction. (Grubb et al. 2020). Emergence delirium and dysphoria are difficult to differentiate and are hypothesized to involve opioids and inhalation anesthesia (Pascoe 2000; Hofmeister et al. 2006). The use of opioids, in this case, fentanyl that was used for intraoperative rescue analgesia, was suspected to be associated with dysphoria/emergence delirium in our study. Therefore, the total dose of fentanyl administered and the time of the last dose of fentanyl administration to extubation were investigated for correlation with the recovery score. The results showed a weak correlation with the recovery score, which was the same direction as the Becker et al. (2013) and Romano et al. (2019) studies. These studies implied that the correlation between fentanyl and recovery quality might not be explicit and that further study is needed with larger sample sizes.

Inhalation anesthesia was investigated for its relationship with poor recovery. Human medicine has revealed that inhalation anesthesia was involved in poor recovery (Kanaya et al. 2014). The present study analyzed the total amount of isoflurane and the time from turning the vaporizer off to extubation to find a relationship with the recovery score. The results showed non-correlation between inhalation anesthesia and the recovery score. These results suggest that isoflurane may not predispose to poor recovery, as shown in previous studies (Tsai et al. 2007; Costi et al. 2014). Anxiety or stress before anesthesia has been reported to be a factor in developing poor recovery quality in children. Higher anxiety levels showed a greater odd

ratio for this complication (Kain et al. 2004). In our study, dogs visiting the hospital showed signs of anxiety, but unfortunately, the anxiety level was not evaluated, and a relationship between anxiety and poor recovery was not determined. Pain has also been suspected to be a predisposing cause of poor recovery (Bednarski 2015). The behavior expressed for dysphoria/emergence delirium, and the behavior expressed from pain may overlap and be hard to distinguish. (Buback et al. 1996; Teixeira et al. 2013). As shown in this study, recovery scores and pain scales are correlated. Dysphoria/emergence delirium requires sedation to resolve the complication, while analgesic drugs are required for pain. Therefore, this study used a drug that provides sedation and analgesic effects (dexmedetomidine) to treat poor recovery.

Another potential complication of concern was paralysis of the contralateral limb. A report of a patient receiving regional analgesia at the lumbar plexus with ESN guidance developed contralateral paralysis (Vettorato et al. 2013). In the present study, the novel ultrasound guidance technique provided the ability to visualize the needle direction while performing the nerve block. This technique decreases the chance of distribution of the local anesthetic to undesirable areas. Therefore, our study has no reports of postoperative paralysis in the contralateral limb.

The present study has limitations that could have confounded the results and interpretation. First, the sample size is small for some important parameters that showed only a trend of difference, such as isoflurane vaporizer settings in each surgical event. Larger sample size in future studies will improve the power and provide more robust evidence. Second, end-tidal isoflurane concentration should have been measured using an agent analyzer to provide better information on the anesthesia requirements. In this study, end-tidal isoflurane was not measured due to the difficulty of sampling when the patient was transported to several different hospital areas using a reliable analyzer. The vaporizers at our institution are calibrated annually using the manufacturer's recommendations. Third, the administration of hydromorphone during the postoperative period before extubation may not be necessary for every case and may mask the actual postoperative analgesic effect of the block. However, the study was designed to provide comfort for all patients, and we considered it necessary for the CON group from prior clinical experience. Fourth, the success of the lumbar plexus and sciatic nerve blocks was not confirmed in this

study, but the success can be inferred from the lower requirement of intraoperative fentanyl. To determine the success of the block, confirmation had to be performed on conscious dogs. The sensory block can be tested by pinching the area where the nerve is supplied and evaluating the response, such as avoidance, vocalization, or limb withdrawal. The motor function can be evaluated by observing the leg position, proprioception, and the ability of the dog to use the blocked limb when walking or standing (O Cathasaigh et al. 2018). Therefore, the success of the block cannot be detected in this study because the patients were under anesthesia. Finally, three unvalidated pain scoring systems were used in the study. The pain scores used in the study consisted of modified MUMPS, VAS, and CSUPS. The modified MUMPS was used in this study due to the reliability of its behavior descriptions for evaluating pain. The modified part is the removal of the respiratory system, cardiovascular system, and pupil size because they do not always represent patient pain (Holton et al. 1998). The VAS was used in the study because it is a sensitive scale that can detect subtle changes in pain and has been used in other studies. (Aghighi et al. 2012; Congdon et al. 2017). The CSUPS system was selected because the scale was used at the institution where surgery was performed. This allowed for evaluator familiarity with the pain scale, leading to consistent pain scoring and decision-making for the administration of rescue analgesia drugs.

5.5 Conclusion

The ultrasound guided, lumbar plexus and sciatic nerve block with this novel approach showed the benefit intraoperative and postoperative analgesic efficacy and safety for patients undergoing TPLO surgery.

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CHAPTER 6: THE FINANCIAL IMPACT OF ULTRASOUND-GUIDED LUMBAR PLEXUS AND SCIATIC NERVE ANALGESIA IN DOGS UNDERGOING TIBIAL PLATEAU LEVELING OSTEOTOMY[2]

Tibial plateau leveling osteotomy (TPLO) is one of the most common treatment options for severe cranial cruciate ligament (CCL) disease (Duerr et al. 2014). Dogs receiving TPLO surgery tend to have better clinical-functional outcomes and a lesser chance of developing osteoarthritis than dogs with other treatments (Beer et al. 2018). Previous studies have shown that 82% of pet owners felt that results from TPLO surgery met their expectations and provided a good level of satisfaction. (Hart et al. 2016). Because of the benefits of TPLO surgery, this technique was commonly recommended by the American College of Veterinary Surgeons (ACVS) Diplomates to treat CCL rupture (Duerr et al. 2014). The approximate number of dogs presented for CCL rupture surgery in the United States in 2003 was 29,186 cases per year. At the time, the surgical cost ranged from US$898 to 1,840 per patient. The estimated US cost for treating CCL disease was approximately US$1.32 billion per year (Wilke et al. 2005).

Another Canadian study estimated the TPLO surgery cost between 2008 and 2013 to be CAN$3,480 to 3,544 per patient (Nicoll et al. 2014). Thus, TPLO surgery has an important financial impact on clients and veterinary hospitals (Wilke et al. 2005). Ultrasound-guided lumbar plexus and sciatic nerve block has been shown to improve patient management by reducing the incidence of hypotension, providing better early postoperative pain, and improved recovery quality, as described in Chapter 5. These advantages are good reasons to adopt the technique for clinical practice. However, from the veterinary practice perspective, these benefits may not be sufficient to embrace the technique without considering the financial aspect. No studies have assessed the economic impact of analgesia and anesthesia requirements during TPLO surgery. The current study was designed to provide economic information on using ultrasound-guided lumbar plexus and sciatic nerve block for TPLO surgery in dogs. The main purpose of this study

[2] Warrit K, Griffenhagen G, Goh C, Boscan P. Financial impact of ultrasound-guided lumbar plexus and sciatic nerve blocks with electrostimulation for tibial plateau leveling osteotomy surgery in dogs. *Vet Anaesth Analg* 2019;46:682-688.

was to improve the regional analgesia technique to provide better anesthesia and analgesia to dogs undergoing surgical treatment for CCL disease. The technique involved ultrasonography and electrostimulation for better guidance and success rate (see Chapter 5). To adopt this new intervention into veterinary practice, information on the financial aspects of the procedure was essential.

Several methods can be used to obtain economic data related to a surgical procedure. The most common cost estimations used are gross and micro-costing methods (Basu 2017). The gross-costing method uses an estimated average cost for each event, such as the cost of postoperative physical therapy or the cost to measure intra-arterial blood pressure. This cost in humans is derived from the national average expenditure that the entities responsible for paying the expenditure, such as Medicare or the national health service (Xu et al. 2014; Basu 2017). It is generally easier and less expensive to obtain gross-costing data, but new intervention studies cannot detect differences in resource consumption (Basu 2017). Micro-costing assesses the costs of a particular patient and every input consumed in preventing or treating the disease. This technique provides better precision of cost estimation by showing the actual cost, utilizing data and cost per unit of resource. The micro-costing method has limitations requiring labor to collect and tabulate all individual costs. In addition, the results may not be generalizable to a larger population because the data was obtained at a particular place and time (Xu et al. 2014; Basu 2017). However, micro-costing can be useful in certain scenarios, especially for studying new interventions (Xu et al. 2014). This method can reduce bias in cost estimation and was recommended for use by the United States Panel on Cost-effectiveness in Health and Medicine (Basu 2017). The present study used the micro-costing method to collect estimated cost data because it provided the most realistic, least biased, and most precise information (Špacírová et al. 2020).

The micro-cost estimation was categorized into fixed and variable costs. Fixed costs do not change by intervention and do not vary in the short run. A common example of fixed cost is the cost of the building, anesthesia machine, or surgical instruments (Shiell et al. 2002; Basu 2017). Variable costs are the costs that change with the use of the resource or the number of patients. Variable costs can be saved if the resource is unused, for example, needles, syringes, medications, and disposable supplies. Variable costs are the major

cost that can be saved or enhanced. This study describes the variable and fixed costs to show the overall monetary aspects when using ultrasound-guided lumbar plexus and sciatic nerve block for TPLO surgery.

The monetary evaluation results will provide details on whether an intervention is financially worth adopting when considered, along with the medical benefits. This information is advantageous for both clients and veterinary hospitals. Clients can decide whether the intervention is worth paying for or not, while veterinary hospitals can use the information for decision-making on whether to adopt an intervention into practice.

This study was performed to determine whether ultrasound-guided regional analgesia for CCL surgery is economically viable to adopt into veterinary practice. The study was designed to analyze the influence of regional analgesia on treatment costs. The study hypothesized that ultrasound-guided lumbar plexus and sciatic nerve block would increase anesthesia and analgesia management costs.

6.1 Materials and methods

The study was approved by Colorado State University Institutional Animal Care and Use Committee and Clinical Board Review Committee (09-1299A). All clients were informed and signed a consent form before enrolling their dog in the study. No similar comprehensive study in the veterinary medicine literature could guide a sample size calculation. Therefore, the same dogs enrolled in the efficacy study in Chapter 5 were used for this treatment cost study. The sample size for the Chapter 5 efficacy study was calculated to identify differences in analgesia and anesthesia requirements, which was based on the difference in visual analog pain scales when performing regional anesthesia for pelvic limb amputation in dogs (Congdon et al. 2011). The sample size calculation was set with a power of 80% and an alpha of 5%. Ten dogs per group were sufficient to identify differences in the visual analog pain scale postoperatively.

6.1.1 Cost analysis calculation

The costs used for economic evaluation were calculated based on the costs to the clients from the veterinary teaching hospital, Colorado State University (Table 6.1). As mentioned above, the micro-costing method was used in this study to gather and calculate the cost based on every input consumed for each patient's treatment. The expense was categorized into fixed or variable costs (Frick 2009; Xu et al. 2014).

In this study, fixed anesthesia costs were identical for all dogs in both groups. Variable costs were expenses that varied for each patient perioperatively. Drug cost calculations were based on the actual amount of drugs used. Isoflurane data was calculated from the liquid volume used for the procedure. The isoflurane vaporizer setting recorded from the beginning until the end of anesthesia was used to make the volume calculations used during the anesthesia process. The isoflurane liquid volume was tabulated according to the following formula.

$$\text{Isoflurane volume} = \frac{\text{Fresh gas flow (mL/minute) x VA (vol\%) x Duration (minutes)}}{\text{Saturated gas volume (mL/mL) x 100 vol\%}}$$

Where VA is the volatile anesthetic concentration, the saturated gas volume for isoflurane is 194 mL from 1 mL of isoflurane liquid (Biro 2014).

The variable cost calculations were not limited to only drugs, equipment, and anesthesia for each patient. The cost of nursing care per patient included general, and extra care was also accounted.

Each drug cost per group was indexed into the cost (US$) per kg. This index cost was calculated from each group's average drug per kg and multiplied by the cost per unit (Table 6.1). The cost was calculated as drug cost per kg to decrease the influence of the dogs' body weight. Moreover, the index cost per kg would multiply with the average body weight to reveal each group's potential cost per dog.

Table 6.1 The cost per unit is the retail cost based on a veterinary teaching hospital, Colorado State University, in 2016.

Variable cost (per vial or unit)	Cost per unit (US$)
Propofol (1%, 20 mL)	13.71
Isoflurane (250 mL)	26.52
Fentanyl (20 mL)	13.37
Lactate Ringer's solution (1 L)	12.01
Colloid (Hetastarch; 500 mL)	29.17
Dopamine (40 mg/mL, 10 mL)	7.49
Dexmedetomidine (0.5 mg/mL, 10 mL)	141.3
Methadone (10 mg/mL, 2 mL)	70.14
Hydromorphone (2 mg/mL, 2 mL)	3.12
Carprofen (50 mg/mL, 20 mL)	96.6
Ropivacaine (0.5%, 30 mL)	11.43
20 mL syringe and extension set	32
Echogenic needle	12.00
Additional nursing care (per day)	25.00
Intravenous catheter replacement	50.00
Extra bandage change	40.00

The anesthesia and analgesia management details for dogs who participated in this study were discussed in Chapter 5. In brief, twenty dogs who received TPLO surgery were enrolled in the study and randomly allocated equally into regional analgesia (RA) or control (CON) groups. Dogs in the RA group received ropivacaine for ultrasound-guided lumbar plexus and sciatic nerve blocks, while dogs in the CON group received sterile saline for the blocks. The anesthesia began with the premedication of every dog who received the same dosage of hydromorphone and atropine. The dogs were induced with propofol to effect and maintained with isoflurane. Before the surgery started, the ultrasound-guided lumbar plexus and sciatic nerve blocks were performed. Fentanyl was used for rescue analgesia, and isoflurane was adjusted for an appropriate anesthesia plane. Carprofen and hydromorphone were administered to control postoperative pain. Poor recovery at extubation was treated with dexmedetomidine. Acepromazine and/or dexmedetomidine were given to calm the patient down during the 12 hours postoperative period. Fentanyl and/or methadone were administered for postoperative analgesia. Additional nursing care was needed for agitated dogs and assisting in walking dogs to the bathroom. The incidence of intraoperative and postoperative complications and treatments were recorded. Anesthesia and complications management protocols were implemented in a stepwise fashion. This allowed every item used for every patient to be collected based on the micro-costing technique. The influence of the nerve block on the requirement of anesthesia and analgesic drugs, the treatment of complications, and professional nursing care that affected each patient's cost were included in the study.

6.1.2 Statistical analysis

Differences in monetary value between the RA and CON groups were analyzed. Anesthesia cost was analyzed using GraphPad Prism 6.07 (GraphPad Software Inc., CA, USA). Data distribution was tested for normality using the Shapiro-Wilk test. Student's t-tests or the Mann-Whitney U test identified differences in continuous variables. Pearson's correlation test determined associations between the cost variables anesthesia duration. Significant differences were considered when $p < 0.05$. Monetary data in the study are presented as the median (range min-max), and the currency used in the study was US$.

6.2 Results

The data collection period was between January 2015 and July 2016. Data were collected from 20 client-owned dogs presented to Colorado State University Veterinary Teaching Hospital (CSU-VTH) for surgical treatment for unilateral cranial cruciate ligament rupture. The dogs' ages ranged from one to eight years. A variety of breeds were represented in the study in both groups. The number of males and females is comparable between groups (see Chapter 5). Similarly, no differences were observed in age or breed distribution between groups. Therefore, there was no reason to anticipate that age, breed, or sex would interfere with the cost analysis results.

The average body weight for the dogs in the RA group was 34.4 ± 4.5 kg (mean ± standard deviation), and for the CON group was 33.5 ± 7.2 kg ($p = 0.7$). Overall, the bodyweight of the 20 dogs in the study was 33.9 ± 6.0 kg. The average body weight of all dogs was used to index and calculate the anesthesia cost per kg to decrease variations when considering individual body weights.

The total cost per patient was gathered from several services, including surgery, anesthesia, radiology, physical therapy, administration overhead, and intermediate care. The total cost was divided into two parts, the fixed and variable costs. The fixed cost would account for all the costs that did not change between individual patients. The variable cost varied between patients.

6.2.1 Fixed cost

The fixed costs in this study were found in surgery, radiology, anesthesia, intermediate care, and overhead costs. The details are shown in Table 6.2.

Table 6.2 Fixed cost for performing TPLO surgery

Service	Details	Cost
Surgery cost	Professional fees and surgical room fees which calculated from the average time for TPLO surgery at the VTH	$1,328
Anesthesia	Medical supplies, medical equipment, intravenous catheterization, fluid administration sets, endotracheal tubes, anesthesia machine, and monitoring equipment use, oxygen, heating devices, and professional anesthetist fees	$129
Radiology	Preoperative radiograph to plan the TPLO surgery and postoperative radiograph to confirm plate, angle, and screw placement	$269
Physical therapy	Cold compression, active joint range of motion, transcutaneous electrical nerve stimulation, and laser therapy	$203
Intermediate care	Room for postoperative recovery, professional intermediate care staff fee (monitoring the temperature, respiratory rate, and pulse rate, assessing the patient's pain, ability to eat, walk, drink, urinate and defecate), and basic supplies for primary postoperative nursing care (rewrapping intravenous catheters or warming equipment and food and water after the full recovery)	$225
Overhead cost	General expenses, energy, maintenance, and personnel costs such as management, registration, and administration	$24.50
	Total	$2,178.50

6.2.2 Variable cost

The variable cost was calculated for each dog and was found in surgery and anesthesia. The surgery variable cost included surgical supplies and TPLO supplies. Surgery and TPLO supplies can vary slightly depending on the supplies used for each case. Surgery supply costs consisted of surgical instrumentation and disposable supplies such as gauze, suture material, and bandaging. Surgery supplies can vary slightly between patients, and in the study, the cost for the RA group was US$158.70 (99.10 - 184.40) (median (min-max) and in the CON group was US$159.40 (112.90 - 175.60) (p = 0.68). TPLO supplies costs vary by the size of the TPLO plate and screws. The TPLO supplies cost was US$550.40 (439.03 – 703.45) in the RA group and US$646.07 (450.45 - 698.82) in the CON group (p = 0.73).

The total anesthesia variable cost included drugs, medical supplies, and nursing care. Details of the drugs used are shown in Table 6.3. The total anesthesia variable cost for every patient, which was calculated based on their original body weight, is shown in Table 6.4. Body weight played a role in the cost calculation. To decrease variations and index the cost, the variable cost was calculated per kg of body weight. In order

to receive the cost per patient, the average body weight for all dogs in the study (33.9 kg) was used to calculate with the cost per kg (Table 6.5). The total anesthesia variable cost consisted of intraoperative anesthesia and analgesia costs, resolving intraoperative complication costs, postoperative sedation and analgesia costs, and costs for nursing care.

Table 6.3 Drug administration at each time point, number of dogs that received drugs, and total drug volume [median (range)] per group. RA refers to dogs that received 0.5% ropivacaine for lumbar plexus and sciatic nerve blocks. CON refers to dogs that received sterile 0.9% saline as a sham for lumbar plexus and sciatic nerve blocks. LRS lactated Ringer's solution; n, number of dogs.

Time point	Drug	RA group (n = 10)		CON group (n = 10)	
		n	Volume (mL)	n	Volume (mL)
Anesthesia	Hydromorphone (Premedication)	10	3.5 (2.5-4.2)	10	3.2 (2.4-4.7)
	Atropine	10	1.6 (0.9-1.5)	10	1.1 (0.9-1.7)
	Propofol	10	15 (6-20)	10	19 (7-21)
	Fentanyl	10	11 (1-21)	10	16 (6-43)
	Isoflurane	10	14 (9-17)	10	14 (10-19)
	LRS CRI*	10	776 (498-1100)	10	710 (360-1350)
	LRS bolus†	4	0 (0-360)	8	295 (0-740)
	Colloid (Hetastarch)	1	0 (0-125)	6	123 (0-185)
	Atropine	7	1.2 (0-2.9)	9	1.5 (0-2.6)
	Carprofen	10	2.19 (2.17-2.2)	10	0.21 (2.08-2.20)
	Hydromorphone (postoperative)	10	0.1 (0.09-0.1)	10	0.1 (0.09-0.1)
	Ropivacaine	10	10.7 (7.5-12.5)	0	0
	Dopamine‡	0	0	6	6 (0-23)
Recover (extubation)	Dexmedetomidine	1	0 (0-0.08)	5	0.03 (0-0.15)
Postoperative	Fentanyl	5	3 (0-20)	9	12 (0-23)
	Methadone	0	0	1	0 (0-0.5)
	Dexmedetomidine	3	0 (0-0.14)	6	0.06 (0-0.6)
	Acepromazine	4	0 (0-0.2)	4	0 (0-0.14)

*LRS administered preoperatively 10 mL/kg bolus and continuous rate infusion of 5 mL/kg/hour during anesthesia
†LRS administered for treating hypotension
‡Dopamine calculated based on mL after diluting with sterile 0.9% saline to 800 mcg/mL

Table 6.4 Anesthesia variable costs for each dog in RA and CON groups. The cost was based on the dog's original bodyweight. RA refers to dogs that received 0.5% ropivacaine for lumbar plexus and sciatic nerve blocks. CON refers to dogs that received sterile 0.9% saline as a sham for lumbar plexus and sciatic nerve blocks.

Dog number	RA (US$)	Dog number	CON (US$)
1	76.76	1	158.74
2	66.28	2	56.84
3	73.25	3	112.90
4	107.59	4	116.44
5	65.94	5	282.41
6	83.95	6	159.08
7	89.72	7	97.85
8	98.46	8	76.24
9	80.11	9	119.16
10	92.29	10	69.39
	82.03 (65.94-107.59)*		114.67 (56.84-282.41)*

*Median (min-max) of the anesthesia variable cost of the dogs based on their original body weight

Table 6.5 Drug volume and items used per dog and anesthesia variable cost index in $US per kg. Dogs received 0.5% ropivacaine for lumbar plexus and sciatic nerve blocks (RA, *n* = 10) or sterile 0.9% saline (CON, *n* = 10). The final variable cost was calculated based on the average body weight of the dogs in the study (33.9 kg).

Time point	Drug	RA group		CON group		*p*-value
		(mL per dog)	US$ per kg	(mL per dog)	US$ per kg	
Anesthesia	Hydromorphone (premedication)	3.5 (2.5-4.2)	0.31 (0.3-0.31)	3.2 (2.4-4.7)	0.31 (0.3-0.31)	0.70
	Atropine	1.2 (0.9-1.5)	0.019 (0.019-0.02)	1.1 (0.9-1.7)	0.019 (0.018-0.02)	0.69
	Propofol	15 (6-20)	0.3 (0.1-0.4)	19 (7-21)	0.3 (0.2-0.5)	0.74
	Fentanyl	11 (1-21)	0.2 (0.03-0.5)	16 (6-43)	0.4 (0.09-0.8)	0.02
	Isoflurane	14 (9-17)	0.04 (0.03-0.06)	14 (10-19)	0.05 (0.03-0.06)	0.27
	LRS*	910 (730-1400)	0.3 (0.2-0.5)	1080 (920-1350)	0.4 (0.3-0.5)	0.04
	Hetastarch	0 (0-125)	0 (0-0.3)	123 (0-185)	0.28 (0-0.3)	0.05
	Atropine	1.2 (0-2.9)	0.02 (0-0.04)	1.5 (0-2.6)	0.02 (0-0.05)	0.06
	Carprofen	2.19 (2.17-2.2)	0.21 (0.21-0.212)	2.18 (2.08-2.2)	0.21 (0.20-0.21)	0.07
	Hydromorphone (Postoperative)	0.1 (0.09-0.1)	0.15 (0.14-0.15)	0.1 (0.09-0.1)	0.15 (0.15-0.16)	0.88
	Ropivacaine	10.7 (7.5-12.5)	0.11	-	0	
	Echogenic needle†	-	12	-	0	
	Dopamine CRI‡	-	0	6 (0-23)	±39.49	
Recover (extubation)	Dexmedetomidine	0 (0-0.08)	0 (0-0.1)	0.03 (0-0.15)	0.05 (0-0.2)	0.09
Postoperative	Fentanyl	3 (0-20)	0.06 (0-0.4)	12 (0-23)	0.3 (0-0.4)	0.31
	Methadone	-	0	0 (0-0.5)	0 (0-0.51)	0.47
	Dexmedetomidine	0 (0-0.14)	0 (0-0.19)	0.06 (0-0.6)	0.09 (0-0.84)	0.22
	Acepromazine	0 (0-0.2)	0 (0-0.002)	0 (0-0.14)	0 (0-0.001)	0.98
Variable cost for average 33.9 kg dog		82.65 (69.15-94.56)		125.8 (55.23-156.35)		

The volume of drugs and cost was shown in [median (range)]. The echogenic needle and dopamine were shown per item or use, respectively.
* LRS, the total volume of lactate Ringer's solution administered.
†Echogenic needle; insulated echogenic needle designed for regional analgesia.
‡Dopamine CRI, the dopamine used during anesthesia, and the cost were calculated from the dopamine per vial, sterile 0.9% saline for dilution, syringe pump use, and 20 mL syringe and extension tube.

The first category of costs was for intraoperative anesthesia and analgesia, which included anesthesia premedication, induction, maintenance, intraoperative fentanyl rescue analgesia, and postoperative analgesia to control pain. Anesthesia premedication consisted of hydromorphone and atropine administered intramuscularly; the dose was similar between groups (p = 0.7 and p = 0.69, respectively). Anesthesia induction was obtained with propofol until endotracheal intubation was achieved. No differences in drug volume or cost between groups were observed (p = 0.74; Tables 6.3 and 6.5). The cost of isoflurane from when the isoflurane vaporizer was turned on until it was turned off was similar between groups (p = 0.27; Tables 6.3 and 6.5). Intraoperative fentanyl rescue analgesia index cost for the RA group was US$0.04 (0.03-0.5) per kg, which was less than the cost in the CON group (US$ 0.4 (0.09-0.8) per kg; p = 0.02; Table 6.3 and 6.5). Before recovery from anesthesia, carprofen and hydromorphone were administered subcutaneously to all dogs (p = 0.66 and p = 0.88, respectively). The echogenic needle (US$12 per dog) and ropivacaine cost (US$0.11 per kg) were two items only applied to the RA group. These two items resulted in the cost of anesthesia and analgesia in the RA group (US$60.52 (48.31-70.02) per dog) being greater than the cost in the CON group (US$49.79 (37.33-63.74) per dog; p=0.02).

The second category of costs included those needed to resolve intraoperative complications. This included the cost of treating bradycardia, hypotension, and poor recovery. Bradycardia, the intraoperative complication most commonly found in the study, developed in seven dogs in the RA group and nine in the CON group. Atropine was used to treat this complication. The cost for atropine was US$0.02 (0-0.04) per kg in the RA group and US$0.02 (0-0.05) per kg in the CON group. There was no significant difference between groups (p = 0.06). Intraoperative hypotension was found in four dogs in the RA group and eight in the CON group. The treatment for this complication was a stepwise protocol described in chapter 5. Treatment costs included fluid therapy and dopamine administration. Fluid therapy included a Lactated Ringer's solution bolus and colloids administration. The cost of using Lactated Ringer's solution to treat hypotension in the RA group (US$ 0.3 (0.2-0.5) per kg) was lower than in the CON group (US$ 0.4 (0.3-0.5) per kg; p = 0.04). The treatment for hypotension with colloids was US$ 0 (0-0.3) per kg in the RA group and US$ 0.28 (0-0.3) per kg in the CON group, which was not different between the groups (p =

0.05). This may be associated with the small number of dogs that received colloids in each group (RA, n=1; CON, n=6; $p = 0.06$). Dopamine administration was calculated based on a vial of dopamine, 20 mL syringe, and extension set. The cost of dopamine for each dog was US$39.49. Six dogs in the CON group required dopamine for the treatment of hypotension, while no dogs received dopamine in the RA group (Tables 6.3 and 6.5). At the time of recovery from anesthesia, one dog in the RA group and five dogs in the CON group had poor recovery from anesthesia and required rescue sedation with dexmedetomidine to treat this complication. Even with the difference in poor recovery incidence, the cost to manage the complication was comparable between the groups ($p = 0.09$; Table 6.5). When combining all complication management, the cost to treat complications per dog was different between groups, with US$11.30 (9.03-24.22) in the RA group and US$63.06 (10.58-66.53) in the CON group ($p = 0.02$; Table 6.6).

The third category of costs was for postoperative sedation and analgesia. During the first 12 hours of the postoperative period, five dogs in the RA group and nine in the CON group required fentanyl for postoperative rescue analgesia. The groups used a comparable amount of the drug resulting in no difference in cost ($p = 0.31$). Methadone was used for rescue analgesia in this postoperative period. None of the dogs in the RA group required methadone, and one dog in the CON group required methadone; there was no difference in cost ($p = 0.47$). Dexmedetomidine was used in three dogs from the RA group during the 12-hour postoperative period and six in the CON group. The drug cost was similar between the groups ($p = 0.22$). Four dogs in the RA group and the same number of the dogs in the CON group received acepromazine for sedation. The drug doses were comparable, resulting in similar costs between groups ($p = 0.98$) (Table 6.5). Each drug in this cost category had a non-significant difference between the RA and CON groups. However, when each dog was added, the cost for postoperative sedation and analgesia was higher in the CON group ($p = 0.02$) (Table 6.6).

The fourth cost was associated with nursing care. During the postoperative period, one dog in the RA group could not balance himself while walking to the bathroom to the point that assistance was required. The dog could walk without aid while returning to the intermediate care ward. The cost for extra nursing care for this dog was US$25. In the CON group, one dog became extremely agitated and restless in the

postoperative period. As a result, the dog removed its incision site bandage and intravenous catheter, which required additional care and replacement supplies. The cost of correcting this incident with a new bandage and intravenous catheter was US$114.00. This was far greater than the costs for other dogs (Table 6.6). However, because this dog was considered an outlier, the additional costs were not included in the financial analyses.

The anesthesia variable cost per dog of the RA group was US$82.65 (69.15-94.56) and in the CON group was US$125.80 (55.23-156.35) ($p$ = 0.02). The difference between RA and CON groups' lowest and highest costs were calculated to reveal the possible loss or saving costs from performing ultrasound-guided lumbar plexus and sciatic nerve blocks. The difference of the lowest possible cost between the RA and CON groups was calculated using the minimum value of the RA group subtracted from the CON group, which resulted in -US$13.92. This indicated of possible loss of US$13.92 by performing the nerve block. The difference of the highest possible cost between the RA and CON groups was calculated using the maximum value of the RA group subtracted from the CON group, which was US$61.79. This indicated a possible saving from performing the nerve block of US$61.79. These savings resulted from the difference in the cost of treating intraoperative complications and postoperative care.

The anesthesia variable cost calculation method in this study differed from what was used in human medicine. The essential factors used to calculate the costs in human medicine are anesthesia duration, patient condition, procedure, and extra drugs and equipment. Anesthesia duration is calculated in terms of cost per unit time, which is a very important factor in human anesthesia (Schuster et al. 2004). In veterinary medicine, anesthesia duration has also been correlated with hospital costs. (Smith et al. 2017) In the present study, anesthesia duration was not associated with anesthesia variable cost (R^2= 0.004; p = 0.79) because both groups had comparable anesthesia durations (p = 0.4). Adding regional analgesia to the procedure only increased the anesthesia duration by 4-5 minutes (Table 5.1). Therefore, anesthesia costs in this study were related to the requirements of drugs, medical equipment, and professional care, not the length of anesthesia time.

Table 6.6 Anesthesia variable cost calculated based on the average body weight of the dogs in the study (33.9 kg). The cost was categorized into RA and CON groups. RA refers to dogs that received 0.5% ropivacaine for lumbar plexus and sciatic nerve blocks. CON refers to dogs that received sterile 0.9% saline as a sham for lumbar plexus and sciatic nerve blocks.

Anesthesia variable cost category	RA (US$)	CON (US$)	*p*-value
Cost for intraoperative anesthesia and analgesia management	60.52 (48.31-70.02)	49.79 (37.33-63.74)	0.02
Cost of resolving intraoperative complications	11.30 (9.03-24.22)	63.06 (10.58-66.53)	0.03
Cost for postoperative sedation and analgesia	3.86 (0-19.81)	17.11 (3.33-40.85)	0.02
Cost of nursing care	0 (0-25)	0	0.99
Total variable cost	82.65 (69.15-94.56)	125.80 (55.23-156.35)	0.02

6.2.3 Client and Veterinary Teaching Hospital Costs

Costs in this study are discussed from two perspectives. The first is the client costs which show the potential price the client has to pay for the dog's greater comfort during and after TPLO surgery. The second is the financial impact of the block on the veterinary teaching hospital costs. In this study, the costs will be presented from both perspectives.

From the client's perspective, the cost the owner has to pay for ultrasound-guided lumbar plexus and sciatic nerve block alleviating the pain during TPLO has two potential directions. The first potential is the potential anesthesia cost saving of US$61.79. This number is calculated from the difference between the highest potential cost between the RA and CON groups. The second potential cost was the additional US$13.92 that the owner would have to pay for the blocks. This additional cost was calculated from the difference between the RA and CON groups' lowest potential anesthesia variable cost.

From the perspective of the veterinary hospital, the financial impacts of the procedure would present in terms of an annual amount to plan for hospital expenditures in each fiscal year. In this institute, the average number of TPLO surgeries per year was 160 cases, which would result in cost savings in anesthesia variable costs of US$9,886.40 per year or an increase of US$2,227.20 per year.

The cost of essential devices is the high impact cost that affects veterinary hospital expenditures for performing ultrasound-guided lumbar plexus and sciatic nerve blocks. These include an ultrasound unit and electro-stimulator nerve finder (ESN) device. The cost for a new ultrasound unit with one probe varies

between US$15,000 to US$29,500. The cost of the machine can be changed by the type and number of the ultrasound transducer probes. In clinical practice, ultrasound is a device that can be used in several service areas. The use of this device in anesthesia service for guiding nerve blocks is one potential channel for the clinic to gain monetary benefit from the machine. Several factors must be considered to determine the potential minimal charge to clients that would be sufficient to cover reimbursement from performing ultrasound-guided lumbar plexus and sciatic nerve blocks (Ginsburg 2012). The cost can be calculated based on the break-even point of the machines. The essential factors included are the machine's purchase price, lifetime, and the number of cases per year. For example, if the machine purchase price were calculated using the same ultrasound unit model used in this study (Fujifilm Sonosite Inc., WA, USA) with one transducer probe, the cost would be US$25,000. The second factor to consider is the lifetime of the machine. Ultrasound machines are fixed assets, and their value declines over time. The time interval the machine functions properly is referred to as the machine's lifetime (Sahu et al. 2016). In this study, the estimated lifetime for the ultrasound machine was six years. The third factor that drives the fee charged for service is the volume of services performed, so the greater the number of patients, the lower the client's cost. The number of cases undergoing TPLO surgery at CSU-VTH was around 160 per year. To calculate the fee charged for the ultrasound service, the fees were calculated using the following formula:

Fee charged for service = Total purchase price/(Estimated unit lifetime x Estimated number of TPLO surgeries per year)

The ultrasound fee service charge = US$25,000/ (6 years x 160 cases/year) = US$26.04.

Based on the number of cases seen at this veterinary hospital, the service fees for using ultrasound-guided regional analgesia per patient should be at least US$26.04 to cover the reimbursement of the machine.

Another device used in this study for performing the regional analgesia was the electro-stimulator nerve finding machine. In the study, the cost for an ESN machine (Stimpod 450; Mila International Inc., KY, USA) was US$925 with a lifetime of 10 years. The number of cases used was 160 cases/year, resulting in the fee for using ESN being US$0.58 per case. The role of the ESN ultrasound-guided technique was to

confirm the proximity of the needle tip and the target nerve. The necessity of using ESN with ultrasound-guided regional analgesia may be in doubt; some studies have shown that ESN was not required when used with ultrasound for the nerve block. Human studies have shown that when ESN was used with ultrasound for nerve blocks, the analgesic efficacy did not improve, and the time to perform the procedure increased (Beach et al. 2006; Dillane & Tsui 2012).

On the other hand, the ESN benefits from a safety point of view. The ESN can be used to confirm when the needle tip has accidentally punctured the nerve, allowing the needle to be repositioned and avoiding the injection of local anesthetic into the nerve (Dillane & Tsui 2012). Not every hospital uses ultrasound-guided with ESN for nerve blocks. The cost for ESN may not be included in every practice that performs ultrasound-guided nerve blocks.

As mentioned above, the fee charged for service is based on the number of patients. Therefore, if the number of TPLO patients increases, the ultrasound and ESN fee costs would decrease and vice versa, as shown in Table 6.7.

Table 6.7 Potential anesthesia and postoperative charges per case with a different number of yearly cases TPLO scenario.

Number of expected cases per year (US$)	Ultrasound fee (US$)	Electrical nerve stimulator fee (US$)	Total utility fee /surcharge per case (US$)
50	83.33	1.85	85.18
100	41.66	0.92	42.58
150	27.77	0.61	28.38
200	20.83	0.46	21.29

The ultrasound and electrical nerve stimulator machines are US$25,000 and US$925. The estimated unit lifetime for ultrasound was six years, and the electrical nerve stimulator machine was ten years. The machine charged calculation is based on the machine cost, number of expected cases per year, and expected lifetime of the machines.

The total anesthesia cost, which affects both clients and veterinary hospitals, was calculated to show the potential cost that the RA and the CON groups can generate. The cost from the RA group was calculated based on the anesthesia and intermediated care fixed cost (US$354), the anesthesia variable cost of the RA

group (US$82.65 (69.15 - 94.56)), and the ultrasound (US$26.04) and ENS cost (US$0.58). The total anesthesia cost of the RA group was US$463.27 (449.77 - 475.18). On the other hand, the total anesthesia cost in the CON group would include the cost of anesthesia and intermediate care fixed cost (US$354) and the anesthesia variable cost of the CON group (US$125.8 (55.23 - 156.35). As a result, without the ultrasound-guided lumbar plexus and sciatic nerve block, the total anesthesia cost would be US$479.80 (409.23 - 510.35). The total anesthesia cost difference between the RA and CON groups was US$16.53 (-40.54 - 35.17). Therefore, from the hospital point of view, the nerve blocks can potentially increase the anesthesia cost to US$6,486.40 per year and save the anesthesia cost by US$5,627.20 per year. The ultrasound-guided nerve blocks generated a difference in total anesthesia cost of 3.6 (-9 - 7.4)%.

The greatest cost affecting the client is the total TPLO cost which is calculated based on all the fixed and variable costs. The total cost to the client for TPLO surgery with ultrasound-guided lumbar plexus and sciatic nerve blocks was US$2,996.87 (2,812.4 – 3,187.53), while the total TPLO cost without the nerve blocks was US$3,109.77 (2,797.08 – 3,209.27). In this study, when comparing the total anesthesia cost with the total TPLO cost, the total anesthesia cost was approximately15% of the total TPLO cost.

From the veterinary teaching hospital's point of view, the total TPLO cost was crucial for revealing the big picture of the procedure. The cost was presented in the term of cost per year, using 160 cases per year for calculation. The total TPLO surgery with ultrasound-guided lumbar plexus and sciatic nerve blocks (RA) was US$479,499.40 (US$449,984.00 – 510,004.80) per year. While the total TPLO cost without the nerve blocks (CON) was US$497,563.20 (447,532.80 – 513,483.20) per year. The difference in total TPLO surgery between receiving nerve blocks and not receiving nerve blocks was US$18,064 (-2,451.2 – 3,478.40) per year.

6.3 Discussion

Ultrasound-guided regional analgesia with electrostimulation confirmation of the lumbar plexus and sciatic nerve can decrease the anesthesia variable cost in most dogs, with some exceptions. The decrease in anesthesia variable cost was due to the lower intraoperative complications management and postoperative sedation and analgesia costs. The decreased total anesthesia cost results in reduced total TPLO costs. This

benefits the client by saving money on the TPLO surgery while having better analgesic efficacy from regional analgesia. This also saves total anesthesia costs for the veterinary teaching hospital.

The variable cost is crucial to show the difference in cost. Twenty percent of dogs in the CON group that did not require additional or rescue support and did not develop complications intraoperative and postoperatively had the anesthesia variable cost close to the dogs in the RA group. In these CON dogs, if they received the peripheral nerve block, the extra cost for regional anesthesia and the use of ultrasound and ESN would not have generated any benefit. In addition, it would have increased anesthesia variable costs by US$13.92 and ultrasound and ESN service fees by US$26.62 per dog. However, most dogs that did not receive regional analgesia required additional rescue drugs, and the quality of anesthesia during recovery and the postoperative period was not ideal.

The lower anesthesia variable cost of the RA group was associated with two cost categories. The first category was the cost of resolving intraoperative complications. The major complication that generated lower costs in the RA group was hypotension. The incidence of hypotension was 40% in the RA group and 80% in the CON group. In the RA group, in hypotensive dogs, in addition to lower isoflurane vaporizer settings, three dogs required crystalloids, and one dog required crystalloid and colloid to restore blood volume and resolve the hypotension. In the CON group, in addition to the lower isoflurane vaporizer setting, two dogs required only crystalloids, but six dogs required crystalloid, colloid, and continuous dopamine infusion to increase myocardial contractility and vascular tone resolve the complication. The greater requirement for treating this complication was the key factor that caused higher anesthesia variable costs in the CON group than in the RA group. Another cost that caused anesthesia variable costs to be lower in the RA group was the cost of postoperative sedation and analgesia. The cost for each drug in the postoperative period was similar, but the cumulative drug cost differed between the CON and the RA groups. Dogs in the CON group tended to have a greater incidence of poor recovery, required postoperative analgesia earlier, and needed additional drugs for analgesia and sedation. This resulted in greater postoperative sedation and analgesia management costs for the CON group.

Anesthesia duration is essential for human studies as it is a major factor in cost calculation (Schuster et al. 2004). In veterinary medicine, additional anesthesia duration can increase final hospital costs (Smith et al. 2017). The nerve block duration in this study was 4-5 minutes (Table 5.2), and the anesthesia duration was not affected, as shown by similar anesthesia duration periods between the RA and CON groups. This study showed that the time to perform the nerve blocks did not alter the cost.

In the present study, anesthesia duration was not correlated with anesthesia variable costs as in human studies. In human medicine, anesthesia cost calculations include professional anesthesia fees per time unit, drugs, and equipment (Schuster et al. 2004). The professional anesthesia fee was included in the anesthesia fixed cost in this study (Table 6.2). The anesthesia variable costs included only drugs, equipment, and nursing care.

The ultrasound unit and the ESN were high-cost assets. Two scenarios were presented for calculating the fee to reimburse the ultrasound and ESN devices. The first scenario calculated the cost based on the assumption of using the machines only for the ultrasound-guided lumbar plexus and sciatic nerve blocks. In the study setting, the fee charged for service had to be at least US$26.62 to cover the cost of the machines. To alter the fee charged for service, the major factor affecting this calculation was the number of cases, as shown in Table 6.7. The greater number of TPLO cases, the lower the charge for nerve block service. This lower cost will benefit the client and the veterinary hospital. However, the hospital can recruit additional TPLO cases only if additional professional services do not need to be added (Schuster et al. 2004). Adding cases and increasing professional services will inflate the hospital budget, and the total TPLO surgery cost may not meet the break-even point. This calculation method was simple to perform, but the ultrasound service fee may be considered overcharging because, in veterinary practice, it would be rare to use ultrasound only for this nerve block. Ultrasound machines can be used for diagnostic purposes and other procedures, such as vascular access or biopsy guidance for aspirations (Mattoon & Nyland 2015; Mattoon et al. 2015; Pavlisko et al. 2018). The second scenario is the calculation of the service fee that is calculated based on every usage of the machine. Using ultrasound for other procedures will decrease the overall service fee charge for each client. This calculation from the actual use in the hospital may reflect

the reasonable cost from the client and hospital's point of view. However, calculating usage data for the entire hospital may be inconvenient, especially for large veterinary hospitals.

These two service fee calculation methods revealed that the ultrasound machine could be used to generate income. The calculation methods showed how to charge to cover the reimbursement of the machine. To create a profit for the hospital, a reasonable additional cost may have to be included in the charge for service.

6.3.1 Other cost analysis for regional analgesia techniques for TPLO surgery

One other study evaluating anesthesia and the cost of regional analgesia for TPLO surgery has been published. (Palomba et al. (2020). In that study, using ESN, levobupivacaine was used for the lumbar plexus and sciatic nerve block. That study showed a cost-saving from the peripheral nerve block, similar to the present study. The saving in that study was found only when the dog's weight was greater than 15 kg. However, dog weight was confounded because the drug cost was calculated per vial. Dogs with weights less than 15 kg were charged for the entire drug vial, and the amount of drug that was not used was wasted. The present study calculated drug cost based on the amount used. Veterinary practices usually administer drugs that come in multiple-use vials to lower the cost and allow the clinic to charge the client for the amount of the drug used. Charging per vial and wasting unused drugs may increase the cost to the client.

6.3.2 Effect of the additional anesthesia cost on the total TPLO cost

From a veterinary hospital's financial perspective, saving costs without compromising patient safety and increasing the standard of care is the ultimate goal. Anesthesia is one of the services that affect hospital costs. In human medicine, it has been reported that the anesthesia cost was approximately 5.6% of the total perioperative cost (Macario et al. 1995). While in the present study, the anesthesia cost was 15% of the total TPLO surgery. In the Marcario study, the lower percentage of anesthesia cost may relate to the difference in the cost proportions of the departments, where the most significant percentages were from the operating room (33%) and the ward (31%). In the present study, the surgery cost was 68%, and the cost of the intrmediate care ward was 8%. While the cost for the intermediate care ward in this study was small, it was associated with the length of the hospital stay. This study's patients usually went home the day after

the surgery. In the Marcario study, inpatients stayed in the ward longer, leading to a larger percentage of the cost in the ward. The proportion of costs from different departments is important for a hospital to know to focus cost-saving efforts appropriately. Larger cost percentage departments have the potential to generate greater cost savings and have more impact on the financial outcome. In this study, 15% of the cost of TPLO surgery amounts to US$67,867.20 per year. The present study showed that performing the blocks potentially decreases total anesthesia costs by 3.6%. This implies that ultrasound-guided lumbar plexus and sciatic nerve blocks for TPLO patients may help save costs and impact the veterinary hospitals' financial system.

Cost determination for specific medical procedures is important from the client's and hospital's perspectives. This study estimated the potential total anesthesia cost for TPLO surgery was US$463.27 (449.77-475.18) from 2015-2016. The cost range was narrow, which allowed the cost estimate to be consistent. The narrow cost range allows the institute to set the cost to the patient at the same amount regardless of individual patient variation. This provides clients with cost fairness. From the hospital's perspective, a more consistent cost estimation allows the hospital to plan a budget strategy more related to the actual situation. This study showed that this cost calculation model benefits clients and veterinary hospitals and can be applied to cost estimations for other surgical procedures.

The cost analysis model of this study was performed in an academic institution which may differ from private veterinary practice. Firstly, in this study, teaching revenue offset some of the veterinary costs. Private veterinary practice does not have this offset option. Secondly, this institution had a high patient volume and the larger volume of drugs used allows for multiple drug packaging. This allows drug costs to be calculated in terms of mL. In the veterinary practice, drug costs may have to be accounted for in terms of cost per vial due to the lower caseload and stock management systems. Therefore, the method of recovering costs may differ in private veterinary practice.

6.3.3 Study limitations

There are three major limitations to consider in this study. First, to provide a non-painful and comfortable recovery, every dog in this study received 0.1 mg/kg hydromorphone after the surgery. In some

dogs, the analgesic effect from the preoperative and intraoperative periods was sufficient for the postoperative period. Hydromorphone administration may exceed the dog's need while increasing drug costs. Second, this study's calculation for the break-even point of the ultrasound and ESN machines was based on a new unit, which may not reflect all scenarios. In the veterinary market, several suppliers provide ultrasound machines with various features with diverse functions, and the choice is dependent on the veterinarian's preferences. Therefore, the model used for the break-even point calculation may not apply in all situations. The third limitation was that the cost calculation of the drugs in this study was based on the amount each dog received. Some veterinary hospitals and most human hospitals will dispense the entire drug vial with clients bearing the cost of the drug that was unused. The method of drug calculation may not directly apply to every veterinary practice, but it can be used as a model for calculating the financial impact of anesthesia costs.

6.4 Conclusions

Ultrasound-guided lumbar plexus and sciatic nerve blocks confirmed by an electro-stimulator nerve finding can potentially increase anesthesia costs. However, in most cases, better analgesia, anesthesia, and decreased complications provide significant cost-saving benefits when regional analgesia is performed for TPLO surgery.

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