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Effect of Peripheral Nerve Blocks in comparison with Epidural Anaesthesia during Tibial Tuberosity Advancement RAPID Surgery: A Case Study

Perifeerse närvi blokaadi mõju võrreldes epiduraalanesteesiaga sääreluuköpruse edendamise operatsiooni ajal: juhtumianalüüs

Final Thesis

Curriculum in Veterinary Medicine

Supervisors: Senior lecturer Aleksandr Semjonov, DVM, PhD

Senior veterinarian Rainer Hõim, DVM

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Pain management is an important and complex subject. Understanding pain physiology and having an effective plan for managing pain is vital for good patient care. To effectively use multimodal analgesia, a good grasp of the major steps of pain transmission and pain pathway is necessary in order the formulate an anaesthetic plan for a pain free state. Intraoperative pain management is a key component of multimodal pain management. Advances and developments within veterinary medicine has been fast, sparking debate over the pros and cons of anaesthetic techniques. As an important advantage, peripheral nerve blocking seeks to manage pain and have a mean alveolar concentration (MAC) sparing effect like epidural anaesthesia, while eliminating the possibility of urinary retention among other anaesthetic complications caused by subdural injection of opioids commonly used in epidural techniques. This study gives insight into the world of peripheral nerve blocks (PNB), as well as reports on a case study where a successful single preoperative femoral nerve block with lidocaine (3 mg/kg) was performed on a patient undergoing elective surgery to correct a cranial cruciate ligament rupture. The patient had no anaesthetic complications and required minimal intraoperative analgesic intervention using a single fentanyl bolus (2 µg/kg).

Keywords: dogs, peripheral nerve blocks, multimodal analgesia, epidural anaesthesia

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Valu leevendamine on oluline aspekt, millele keskendutakse meditsiinivaldkonnas üha enam. Selleks, et patsientidele pakkuda parimat võimalikku abi, on vaja mõista valu füsioloogiat ja omada tõhusat valu leevendamise strateegiat. Üks oluline lähenemine valu leevendamisele on multimodaalne analgeesia, mis hõlmab mitmeid erinevaid meetodeid valu leevendamiseks. Selleks on vaja mõista valu edastamise peamisi etappe ja valu teekonda organismis, et koostada tõhus valu leevendamise plaan. Intraoperatiivne valu leevendamine on oluline osa multimodaalsest valuleevendamisest. Ühe olulise eelisena perifeersete närvide blokeerimisel on võime valu kontrollida, vähendades samal ajal keskmist alveolaarkontsentratsiooni (MAC) ja vähendades seeläbi vajadust teiste valu leevendavate ravimite järele, näiteks opioidide järele, mis võivad põhjustada mitmeid anesteesiaga seotud komplikatsioone. Antud uuring keskendub perifeersete närvide blokeerimisele (PNB) ning annab ülevaate ühest juhtumist, kus üksik perioperatiivne reie närvi blokaad lidokaiiniga (3 mg/kg) viidi läbi patsiendil, kellele oli vaja kraniaalse ristatisideme rebendi korrigeerimiseks teha operatsioon. Patsiendil ei esinenud seoses anesteesiaga komplikatsioone ning ta vajas minimaalset intraoperatiivset analgeetilist sekkumist, kasutades üksikut fentanüüli boolust (2 µg/kg).

Märksõnad: koerad, perifeerne närvi blokaad, multimodaalne analgeesia, epiduraalanesteesia

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LIST OF ABBREVIATIONS

AMPA – alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid

ASA – American Society of Anaesthesiologists

CCL – cranial cruciate ligament

CNS – central nervous system

CRI – constant rate infusion

DBP – diastolic blood pressure

EPI – epidural anaesthesia

FLK – fentanyl lidocaine ketamine

HR – heart rate

IASP – the International Association for the Study of Pain

IM – intramuscularly

IV – intravenously

L – lumbar vertebrae

MAC – mean alveolar concentration

MAP – mean arterial blood pressure

MMA – multimodal analgesia

NMDA - N-methyl-D-aspartate

RR – respiratory rate

S – sacral vertebrae

SBP – systolic blood pressure

SC – subcutaneously

TTA RAPID – tibial tuberosity advancement RAPID

TPLO – tibial plateau leveling osteotomy

PAG – periaqueductal grey matter

PNB – peripheral nerve blocks

WSAVA – World Small Animal Veterinary Association

INTRODUCTION

In the past, it was commonly believed that animals perceive pain differently than humans, or no pain at all. Today, pain management is very different to what it once was in human and veterinary medicine (Hellyer et al., 2007; Gruen et al., 2022). The study of pain is a complex subject. Paying attention and understanding how to manage pain is fundamental for medicine and every aspect of good patient care (Mathews et al., 2014). Just as in humans' varied tolerances for pain, it is believed by owners and veterinarians that similar breed-level differences apply in dogs (Gruen et al., 2020). At its core, pain is a subjective emotion, which often disregards our normal ways of defining it and cannot always be explained by medicine. Nevertheless, what modern science can achieve is to try and manage the conscious experience of pain to the best of our current ability (Mathews et al., 2014).

Cranial cruciate ligament (CCL) rupture is a frequent ailment of large and giant breed dogs. The most common cause for the injury is degeneration of ligaments within the joint and trauma. Management of it is crucial for quality of life and to ensure hind limb use of the affected leg and to alleviate pain. Non-surgical management is rarely recommended as dogs weighing more than 15kg have a poor chance of becoming clinically normal, therefore surgical intervention with various techniques is often preferred. It is known that pain during and postoperatively is a major factor in patient recovery, hence adequate preoperative and intraoperative analgesia is vital (Mathews et al., 2014). This review wants to shed light on modern intraoperative pain management tools and on the possible benefits and use cases of peripheral nerve blocks (PNB) and epidural anaesthesia (EPI) over the other in hind limb surgery. Additionally, the author wants to build upon the previous work performed by Holmberg (2022), where the effects of EPI on pain response during tibial tuberosity advancement RAPID (TTA RAPID) surgery was evaluated, by the use of a case study of a patient that received a single femoral nerve block prior to surgery.

1. LITERATURE REVIEW

1.1 Pain response and pain physiology

Pain management in veterinary medicine has become a cornerstone in quality and compassionate care. As the patient is unable to advocate for itself, it is the responsibility of the veterinary team to recognise pain and suffering and to treat it to the best of our ability. To have effective perioperative pain management it is important to understand the physiology of pain. How pain is transmitted from the stimulated area to the central nervous system (CNS), and how each analgesic is used to its full potential, in addition to the modalities pros and cons, is key to good management of pain.

The International Association for the Study of Pain (IASP) currently defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." (Raja et al., 2020). As in human medicine, even more so in the veterinary profession, the emotional and sensory aspects are difficult to understand. Keeping up to date, following modern approaches and techniques of pain management help the veterinarian to strive towards that pain free state in a patient (Hellyer et al., 2007; Mathews et al., 2014; Gruen et al., 2022).

The World Small Animal Veterinary Association (WSAVA) Global Pain Council classifies pain into two main categories, either acute or chronic. Separating the two is primarily based on time of onset. Chronic pain being defined as affecting the patient for more than three months or lasting beyond the normal time of healing. In contrast, acute pain commonly being associated with tissue damage or the threat of tissue damage, as to purposefully with a reaction to avoid or minimise injury (Mathews et al., 2014). In patients suffering from chronic pain, a comprehensive and multidisciplinary approach must be relied upon to achieve quality of life. Treatment of acute pain should aim towards solving the underlying cause, with the help of managing the nociceptive sensory system (Mathews et al., 2014).

A stress response due to pain is one of many negative effects a practicing veterinarian may encounter. As a reaction to pain the body increases heart rate, increases blood pressure, and decreases gastrointestinal motility mediated by an elevation in inflammatory mediators, catecholamines, and cortisol. More importantly, pain leads to delayed healing and sleep deprivation which are detrimental to the general well-being of an animal as well as people (Brennan et al., 2007; Hellyer et al., 2007). As cats and dogs share a similar nervous system to humans, parallels with human literature and research are commonly drawn in veterinary medicine when considering pain. Numerous studies have

demonstrated other adverse effects of pain on the body. Urinary retention, impaired coagulation and clotting ability, and a decreased immune function are suboptimal features for patient recovery. In the respiratory system, atelectasis, arterial hypoxemia, hypercapnia, ventilation-to-perfusion mismatching, and pneumonia have been seen to be promoted by pain (Brennan et al., 2007; Hellyer et al., 2007). Additionally, to the effects mentioned earlier, pain has been shown to produce myocardial ischemia and cardiac dysrhythmias in the cardiovascular system (Campoy and Read, 2013; Read et al., 2024).

Chen et al. (2019) argues that differentiating between the terms nociception and pain is worthwhile, as nociception refers to detection of noxious stimuli by nociceptors and its transmission and transduction to the brain. While pain refers to the product of higher brain centre processing and involves the emotional and sensory experience that comes with it. Nociception can occur without being aware of pain, and pain can be present without measurable noxious stimulus. During surgery, in an anaesthetised patient with inadequate pain management, nociception and activation of pain pathways occur. This is commonly seen as an increase in heart rate and respiratory rate but is not necessarily perceived as pain by the patient due to being unconscious. Therefore, a multimodal analgesic approach is important to avoid pain perception while in recovery (Self, 2019).

At a cellular level, the response to acute pain is a result of noxious stimulus, mediated by a high threshold nociceptive sensory system. This system is inherently plastic and dependent on disease status, the sensitivity of an injured or inflamed region is further enhanced so that the normally innocuous stimuli, in addition to the noxious stimuli, is perceived as painful (Mathews et al., 2014). Hence, for effective utilisation of multimodal analgesia (MMA), it is important to understand the major steps of pain transmission and the pain pathway (Self, 2019).

Pain physiology can be divided into four processes: transduction, transmission, modulation, and perception (Figure 1). During the transduction, initiated by mechanical, thermal, or chemical stimulus, afferent nerve endings participate in translating noxious stimuli into nociceptive impulses. Transduction is the process where the stimuli are converted into an electrical signal at the stimulus-gated ion channels of nociceptors (Self, 2019). The nociceptor end terminals that bathe in a chemical milieu are found in the skin, muscle, bone, joints, and viscera, and allow for peripheral sensitisation, pain perception and localisation (Duke-Novakovski et al., 2016; Chen et al., 2019). The information is carried from the nociceptors by the primary afferent nerve fibres, which are mostly slow transmitting unmyelinated C-fibres, carrying dull and/or burning pain sensation, and thinly myelinated fast transmitting A-delta fibres carrying thermal and mechanical information (sharp pain sensation)

(Mathews et al., 2014; Self, 2019). Different afferent nerve fibres possess different activation thresholds at their nociceptive terminals, the myelinated A-delta fibres have mechanical and thermal nociceptors that have higher thresholds than touch sensitive A-beta fibre receptors. C-fibres possess even higher activation thresholds than A-delta and respond to all three stimulus types, while A-delta responds to thermal and mechanical stimuli (Mathews et al., 2014).

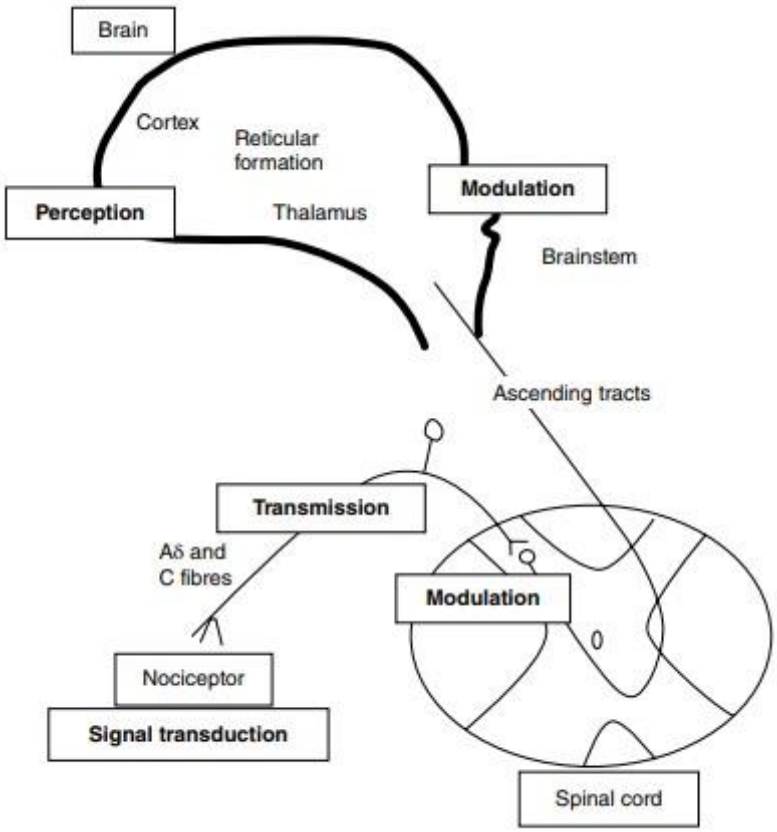


Figure 1. Simplified pain pathway. (Dugdale et al., 2020. Veterinary anaesthesia: principles to practice, second edition).

During transmission, nociceptive impulses are transmitted via primary afferent nerves to the dorsal horn of the spinal cord, from where the impulse is projected into the brain. The dorsal horn has been divided into six physiological zones (laminae I-VI). C- and A-delta fibres terminate in large to the more superficial laminae I-II, although C-fibres tend to communicate deeper via interneurons. As far as we know, nociceptive impulses may elicit three things when reaching the spinal cord. An impulse may cause a fast withdrawal response to the spinal/segmental reflex, an impulse may be projected to the brain via spinoreticular and spinothalamic tracts, or the impulse may be processed/modulated (Self, 2019). Primary afferent nerves synapse to different postsynaptic cell types with the help of numerous neurotransmitters. Instant nociceptive stimuli delivered to the brain, is primarily mediated through the key excitatory neurotransmitter glutamate, and alpha-amino-3-hydroxy-5-methyl-4-isoxazole

propionic acid (AMPA) receptors on dorsal horn neurons. If the afferent C-fibre impulse is highly repetitive or persisting, N-methyl-D-aspartate (NMDA) and metabotropic glutamate receptors are also activated, which greatly amplify the excitability of the central nociceptive neuron, leading to central sensitisation (Figure 2) (Duke-Novakovski et al., 2016).

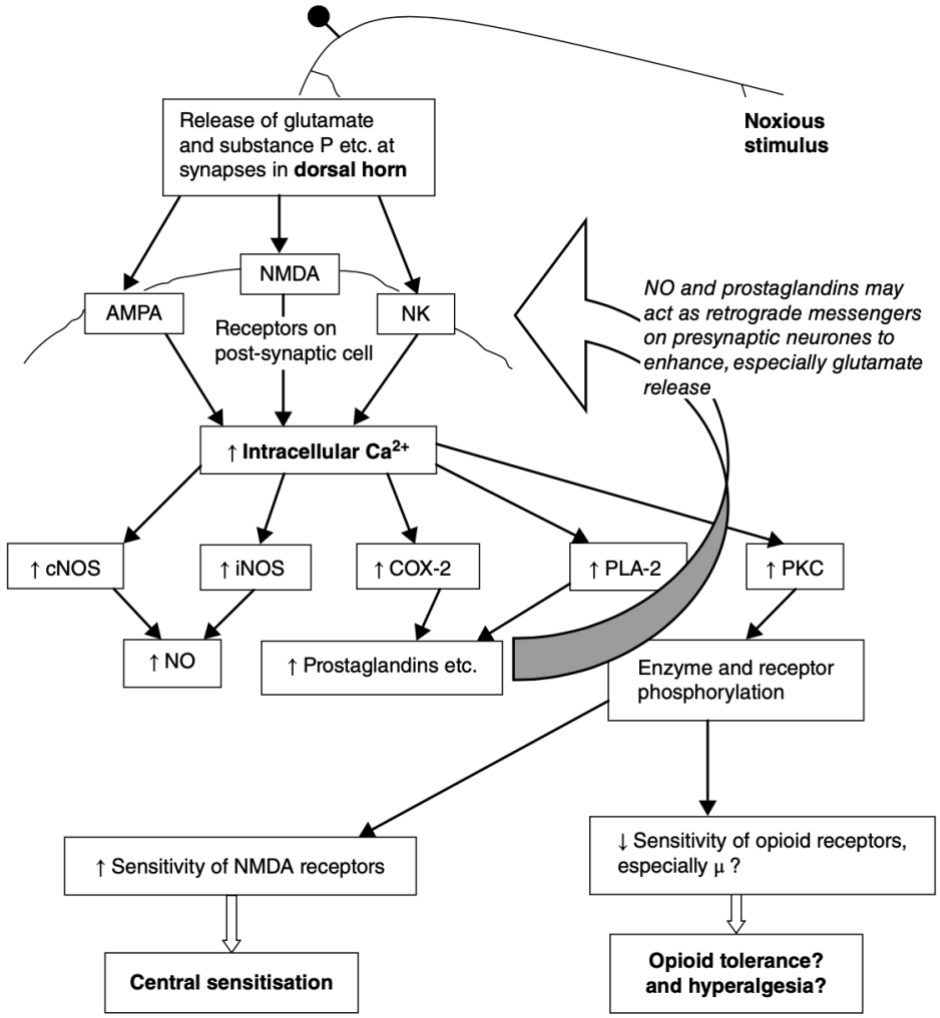


Figure 2. Pathway of central sensitisation. NMDA and AMPA receptors are glutamate receptors; NK1 (neurokinin 1) receptor is a substance P receptor. cNOS, constitutive nitric oxide synthase; iNOS, inducible intric oxide synthase; COX-2, cyclooxygenase 2; PLA2, phospholipase A2; PKC, protein kinase C; NO, nitric oxide. (Dugdale et al., 2020. Veterinary anaesthesia: principles to practice, second edition).

Modulation, which mainly takes place in the dorsal horn, is the complex process of amplifying or dampening the afferent nociceptive impulses. Nociceptive components such as peripheral sensitisation, dorsal horn gating, central sensitisation/wind-up, descending inhibitory- and facilitatory pathways are all modulating the afferent signal (Self, 2019). Tissue injury or inflammation causes changes in the chemical milieu and a form of modulation of nociceptor end terminals resulting in peripheral sensitisation, the damaged cells release a barrage of chemical mediators, collectively referred to as the 'inflammatory soup', which have a variety of peripheral effects (Basbaum et al.,

2009). Agents such as adenosine directly activate the nociceptor, while on the other hand prostaglandins sensitise the nociceptor so that repetitive stimuli are amplified (Duke-Novakovski et al., 2016). This response to injury and inflammation, commonly contributing to hyperalgesia (When noxious stimuli generate an exaggerated pain response), results in long-lasting functional changes in peripheral nociceptors (Self, 2019). Another common term of heightened sensitivity is 'wind-up' pain, used to describe altered central and peripheral pain thresholds where pain is experienced in areas unrelated to the original source. Wind-up leads to an increase in acute pain (Duke-Novakovski et al., 2016). Central sensitisation has been documented in dogs with osteoarthritis due to cruciate ligament disease and should be considered in all cases of chronic pain (Dugdale et al., 2020).

Events that cause brief but intense noxious stimuli, such as a surgical incision or nerve injury, may sensitise nociceptive transmission in the dorsal horn to produce central sensitisation. This leads to a significant decrease in the response threshold in the central neurons, and repeating signals are further amplified (Mathews et al., 2014). Central sensitisation is more commonly thought to produce allodynia, which refers to non-painful stimulus eliciting pain (Self, 2019). Analgesic agents administered before, rather than after, the afferent barrage and central sensitisation has been theorised to be more beneficial for pain management and is the rationale behind pre-emptive analgesia (Duke-Novakovski et al., 2016).

Descending modulatory pathways arise mostly from the brain, more specifically from the cortex, and thalamus, the periaqueductal grey matter (PAG) of the midbrain, the nucleus raphe magnus in the pons, and medulla oblongata. These inhibitory pathways are poorly understood, yet relevant to mention as for example the PAG is thought to be important in opioid mediated analgesia, due to its high concentration of opioid receptors. Although descending inhibition influences many levels of the central nervous system, the most potent and key area is agreed to be the spinal level (Self, 2019).

Pain can be further classified into visceral and somatic pain, where the latter is more of relevance in a surgical setting. Visceral pain is mainly carried by more sparsely distributed C-fibre nociceptors and is therefore duller in nature and poorly localised. Somatic pain is activated by cutaneous and deep tissue nociceptors. A surgical incision in the skin causes a highly localised impulse of sharp pain, while deep tissue somatic pain from the joint, tendons and bones typically elicits throbbing or aching less localised pain (Self, 2019; Chen et al., 2019).

1.2 Multimodal analgesia

Multimodal analgesia (MMA) can be defined as the use of more than one pharmacological class of analgesic medication targeting different receptors along the pain pathway with the goal of improving analgesia while reducing individual class-related side effects. Schwenk and Mariano (2018) suggest that a good MMA protocol is a checklist rather than a recipe. A thought-out protocol should target different receptors along the nociceptive pathway. Depending on the surgery, perioperative pain consists of multiple different subtypes and therefore cannot be effectively treated with a single medication. MMA gives flexibility to the anaesthesiologist to consider patient comorbidities, as well as, to the best of their ability, avoiding the perception of pain (American Society of Anesthesiologists Task Force on Chronic Pain Management, 2010; Schwenk and Mariano, 2018; Gruen et al., 2022).

In a surgical setting, it has been widely accepted that a pre-emptive approach is most effective at managing acute pain, meaning administration of analgesics prior to the start of surgery. A pre-emptive approach, in an analogous way, can be applied to chronic pain, where treating as early in the disease process as possible to prevent adverse effects of ongoing noxious input. The effect of a pre-emptive approach is determined using a pro-active approach to pain management. Meaning for the clinician, as well as the veterinary team, to take pro-active steps to assess for pain and understanding when pain may be present in the patient, while also educating and engaging owners about pain assessment. Pro-active approach additionally includes implementation of measures that slow progression of chronic disease e.g., body condition management of dogs at risk for CCL rupture or osteoarthritis (Gruen et al., 2022).

Regional anaesthesia and analgesia are a cornerstone of MMA, where the use of local anaesthetics facilitate deliberate localised blocking of nociceptive stimuli. Specific and powerful ability of local anaesthetic drugs is that they prevent noxious stimuli from reaching the central nervous system, compared to drugs such as opioids that modulate pain impulses once they reach the CNS (Grubb and Lobprise, 2020). Techniques like PNB and EPI are extensively used and effective components of MMA (Lamont, 2008). Incorporating regional nerve blocks into surgery of the limbs can be highly effective in providing analgesia, while minimising the need for opioids, although the techniques do carry their own risks (Schwen and Mariano, 2018). Use of local anaesthetics will also have a mean alveolar concentration (MAC) sparing effect on the inhalant agent during anaesthesia, which can be advantageous for the cardiovascular system (Self, 2019).

As an example, for a simplified analgesic plan, would have a local anaesthetic acting on peripheral nociceptors and primary afferent nerve fibres, with the help of an alpha-2-agonist. Opioids target the dorsal horn, thalamocortical structures and descending inhibitory pathways, with help from the alpha-2-agonist. Inclusion of non-steroidal anti-inflammatory drugs would minimise and control development of peripheral sensitisation, while drugs such as ketamine would alleviate central sensitisation with its NMDA receptor antagonistic properties (Lamont, 2008).

1.3 Peripheral nerve blockade

Peripheral nerve block has been shown keen interest for the past two decades by the scientific community (Campoy and Read, 2013; Portela et al., 2018; Read et al., 2024). In human medicine, loco-regional anaesthesia is widely used to provide intra- and postoperative pain management (Campoy and Read, 2013; Read et al., 2024). In a recent survey conducted by Parker et al. (2023), the preference of locoregional anaesthesia and analgesia for use in dogs undergoing tibial plateau leveling osteotomy (TPLO) by board-certified veterinary anaesthesiologists was reported, the result was that 79% of the diplomates preferred PNB over lumbosacral epidural.

At its infancy, anaesthesiologists relied mostly on their knowledge of anatomy to localise the target nerve. Later, anaesthesiologists came to be governed by the proclamation of Moore “no paraesthesia, no anaesthesia”. Meaning that in practice, reliance on reports of paraesthesia or nerve tingling from their human patients was used to determine the success of the block (Campoy and Read, 2013; Read et al., 2024). However, in 1993, proponents of newer nerve stimulation techniques, Gentili and Wargnier, reported on paraesthesia techniques and the associated risk of nerve trauma. Their countering statement of “no paraesthesia, no dysasthenia” is perhaps more in line with what modern nerve localisation techniques strive for (Dillane and Tsui, 2012).

The first portable transistorised nerve stimulator was introduced in 1962 by Greenblatt and Denson. Development of new nerve locating technologies has sparked global interest and growth in medical nerve blocks. Nerve stimulation enabled the anaesthesiologist to locate the target nerve more accurately by visualising the stimulated muscle contractions before injecting the local anaesthetic. Even though nerve stimulation was seen to decrease the incidence of nerve trauma, the occurrence still could not be fully mitigated (Dillane and Tsui, 2012; Campoy and Read, 2013; Read et al., 2024).

Today, ultrasound guidance and nerve stimulation have become the new gold standard tools for nerve localisation in people (Campoy and Read, 2013; Read et al., 2024). What was an exclusive realm of the specialist, now with the recent advances of ultrasound guidance, have been monumental for bringing new RA techniques into daily practice (Figure 3) (Dillane and Tsui, 2012). To finally be able to visualise the target nerve and needle placement have negated the disadvantages caused by individual patient anatomy on landmarks, and to avoid the once sought-after paraesthesia more reliably, has been shown to increase the success rate of PNB. However, debate over the role and performance of both techniques is ongoing (Campoy and Read, 2013; Read et al., 2024).

Figure 3. An ultrasound transducer positioned for a sciatic nerve block in a dog. (Read et al., 2024. Small animal regional anesthesia and analgesia.)

Although minimal changes have happened in the practice of neuraxial anaesthesia, the philosophy, and techniques in PNB has seen significant advancement in a brief time, especially in the field of veterinary medicine as procedures and techniques originally described for people are now being adapted to different animal species (Campoy and Read, 2013; Read et al., 2024). Studies in humans have shown that PNB may reduce the risk of complications while still providing excellent analgesia (Campoy et al., 2012).

In a study conducted by Campoy et al. (2012), comparing bupivacaine sciatic and femoral nerve blocks versus bupivacaine and morphine EPI for stifle surgery in dogs, found that peripheral nerve blockade may offer advantages such as avoiding urinary retention and decreasing the amount of opioid consumption over the 24 hours postoperatively, while EPI might be associated with lower isoflurane

requirement but lower systemic blood pressure. Ferrero et al. (2021) also found in their study that dogs that received EPI were at a significantly higher risk of intraoperative hypotension and urinary retention postoperatively, although EPI provided slightly better analgesia compared to certain blocks. Boscan and Wennogle (2016) found that PNB are a good alternative to EPI, due to the potential to improve recovery quality as bladder control and motor function of the contralateral limb are not affected, while also decreasing systemic drug-induced complications, such as hypotension, respiratory depression, bradycardia, and prolonged sedation when waking up from anaesthesia.

1.1.1 Basics of neurophysiology and electrophysiology

For a veterinary surgeon to effectively use nerve stimulation, basic knowledge of relevant electrophysiology is necessary. To be concise, all living cells, including nerve and muscle cells, have a membrane potential. Typically, the membrane potential, measured from the outside to the inside, has a resting potential of around -90 mV. Depolarisation of this resting potential to the threshold level of around -55 mV, results in an action potential along the nerve fiber (Campoy and Read, 2013; Hadzic, 2017; Read et al., 2024).

Electron movement between two points occurs from the anode (positive) towards the cathode (negative). Electrostimulation is facilitated by a nerve stimulator, a special stimulating needle (cathode), and a grounding electrode (anode). When the stimulating needle, approaches a nerve carrying motor fibers, depolarisation occurs, eliciting an action potential and synchronous contractions in the effector muscles that are innervated by the nerve. The negative polarity is beneficial to effectively depolarise the nerve membrane from outside the cell, due to removing the positive charge from outside of the membrane, decreasing the potential across the membrane toward the threshold level, requiring half the electrical current in contrast to if the polarity was switched. Nerve fibers are selectively stimulated depending on their size and thickness, hence the myelinated motor nerves with larger diameter axons can be stimulated at lower currents than smaller poorly myelinated sensory nerves (Campoy and Read, 2013; Hadzic, 2017; Read et al., 2024).

1.1.2 Relevant anatomy of pelvic limb peripheral nerve blocks

The pelvic limbs are innervated by the lumbar and sacral nervous plexuses, which are formed by the ventral branches of lumbar vertebrae (L) L4, L5, L6, L7 and sacral vertebrae (S) S1, with some contribution from L3 and S2 (Figure 4) (Campoy and Read, 2013; Portela et al., 2018; Read et al., 2024). Hence the nerves in charge of the innervation of the canine stifle are saphenous, femoral, obturator, and sciatic. In detail, the stifle joint is innervated by the posterior articular nerve and lateral articular nerve, which are branches of sciatic nerve, and the medial articular nerve, which mainly originates from the saphenous nerve and branches of the femoral and obturator nerves (Di Franco et al., 2023). For invasive stifle surgery, literature indicates that to provide effective surgical analgesia, both the femoral and sciatic nerve should be adequately blocked. This is facilitated by femoral and sciatic nerve blocks, which are minimally invasive and associated with a low rate of complications. Alternative block combinations, which show promise of minimising motor impairment, are being actively researched (Campoy and Read, 2013; Portela et al., 2018; Di Franco et al., 2023; Read et al., 2024).

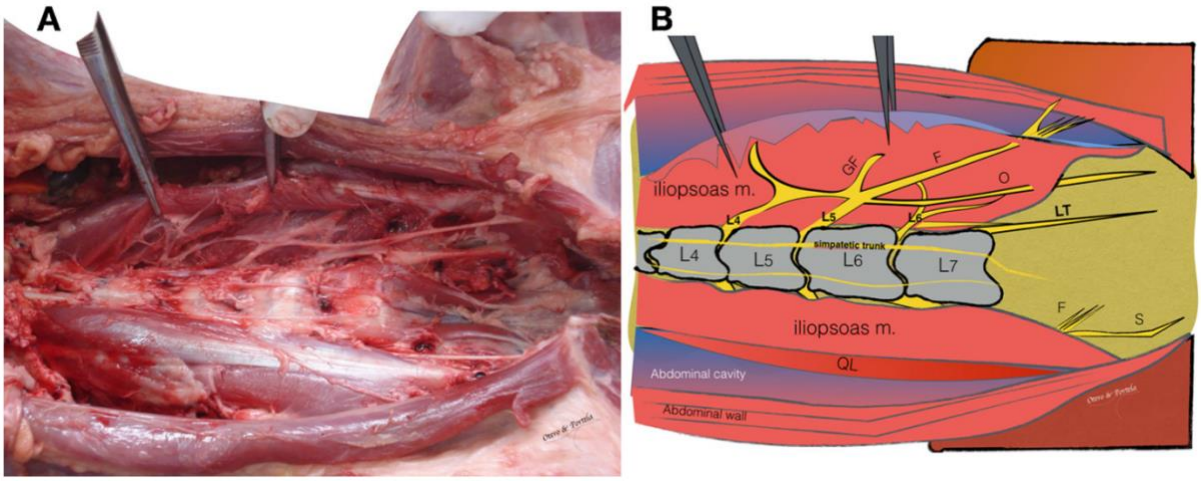


Figure 4. (A) Ventral view of a dissected lumbar region. (B) Schematic representation of the structures observed in (A), note the ventral branches of the lumbar spinal nerves converging to form the lumbar plexus. F, Femoral nerve; GF, Genitofemoral nerve; LT, Lumbosacral trunk; O, Obturator nerve; QL, Quadratus lumborum muscle; S, Saphenous nerve. (Portela et al., 2018. Regional anesthetic techniques for the thoracic limb and thorax in small animals: A review of the literature and technique description).

The femoral nerve, formed by ventral branches of L4, L5 and L6 spinal nerves, arises from the cranial portion of the lumbar plexus. The femoral nerve continues distally through the centre of the iliopsoas muscle and exits at the distal end. At this level we can delimit the femoral triangle, where the femoral nerve gives rise to the muscular and cutaneous branches of the saphenous nerve that supply the sartorius muscle. In the triangle, the iliopsoas muscle is found proximally, the pectineus muscle

caudally and the sartorius muscle cranially. The femoral nerve is located cranial to femoral artery and vein (Figure 5) (Campoy and Read, 2013; Portela et al., 2018; Read et al., 2024).

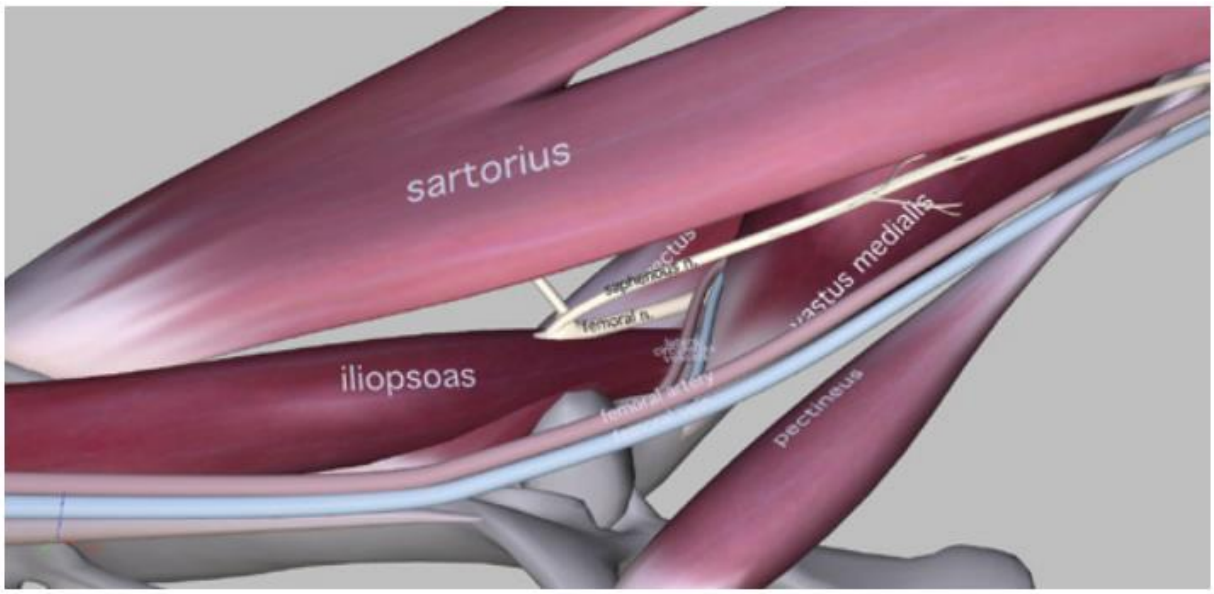


Figure 5. A tri-dimensional rendering of the left femoral triangle from a ventral position, demonstrating the delimitation of the triangle by the iliopsoas muscle proximally, pectineus muscle caudally, and the sartorius muscle cranially. The femoral nerve is located within the triangle cranial to the femoral artery and vein (Campoy and Read, 2013. Small Animal Regional Anesthesia and Analgesia).

The sciatic nerve is formed by ventral branches of L6, L7 and S1 spinal nerves. The nerve courses between the middle and deep gluteal muscles and exits through the greater sciatic notch. When the sciatic nerve leaves the pelvic region, it lies between the superficial gluteal muscle laterally and the gemelli and quadratus femoris muscles medially (Figure 6). Continuing ventrally, the nerve descends between the greater trochanter and the ischiatic tuberosity, where it gives rise to muscular branches that supply the caudal thigh muscles. Here the caudal gluteal artery and vein lie caudal to the muscular branches. The sciatic nerve lies just distal to the greater trochanter and ischiatic tuberosity, between biceps femoris muscle laterally and the semimembranosus muscle caudal and medially (Campoy and Read, 2013; Read et al., 2024).

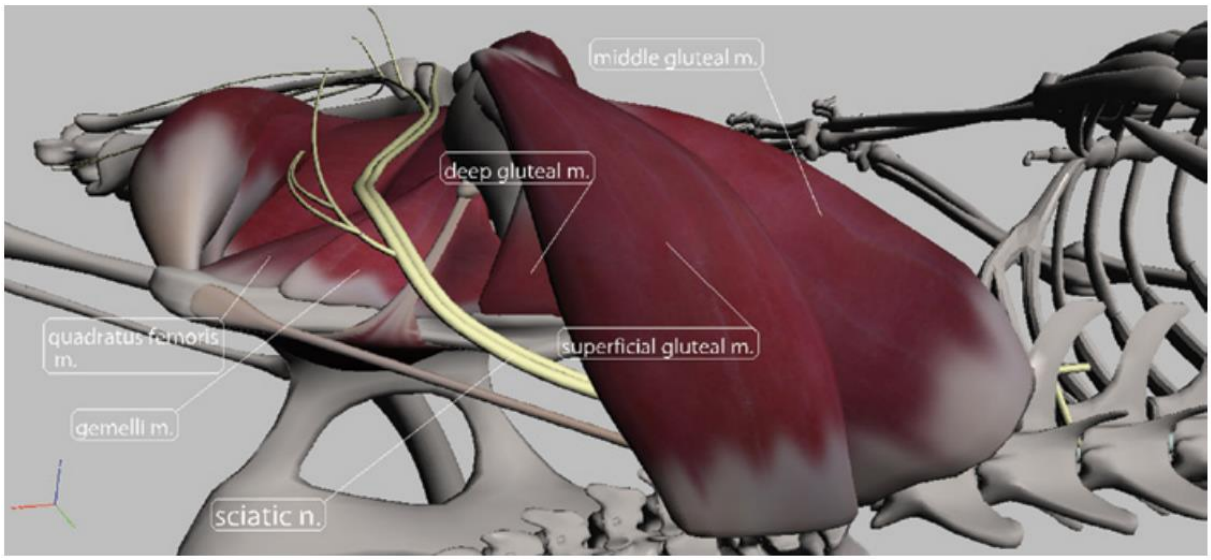


Figure 6. A tri-dimensional rendering of the sciatic nerve of a dog from a dorsoventral view. The sciatic nerve runs between the middle and deep gluteal muscles and exits the pelvis through the greater sciatic notch. The sciatic nerve lies between the superficial gluteal muscle laterally and the gemelli and quadratus femoris medially as it leaves the pelvic region (Campoy and Read, 2013. Small Animal Regional Anesthesia and Analgesia).

1.1.3 Techniques

Nerve stimulation guided femoral nerve block has been described with two different approaches (Campoy, 2008; Mahler and Adogwa, 2008; Portela et al., 2013). The chosen technique depends on preference and clinician experience, however Campoy technique (Campoy, 2008; Duke-Novakovski et al., 2016) seems to be more commonly adopted. Some blind techniques for an inguinal approach have also been described, however techniques utilising nerve stimulation are reported to be more precise at nerve localisation and reduce the risk of iatrogenic nerve damage (Portela et al., 2018).

Using Campoy technique, the patient is positioned in lateral recumbency with the limb to be blocked uppermost and abducted 90 degrees and extended caudally (Figure 7). After clipping and aseptic preparation the inguinal area, the femoral artery should be located by palpating the femoral pulse. The femoral nerve runs cranial to the femoral artery, within the femoral triangle (Figure 8). The stimulating needle is inserted in a 20–30-degree angle parallel and cranial to the femoral artery, with the current initially set to 1 mA (Figure 9). Contractions of the quadriceps muscle and stifle extension can be seen when the needle tip is close to the femoral nerve. At this level, the current should be decreased gradually to the threshold current of 0.4 mA in 0.2 mA increments, while looking to elicit the same response throughout the range. The femoral nerve lies 0.5 – 1 cm under the skin in mid-sized dogs and care should be taken not to insert the stimulating needle too deep, possibly damaging the nerve (Campoy and Read, 2013; Duke-Novakovski et al., 2016; Read et al., 2024).

Figure 7. A dog positioned for a femoral nerve block (Campoy and Read, 2013. Small Animal Regional Anesthesia and Analgesia).

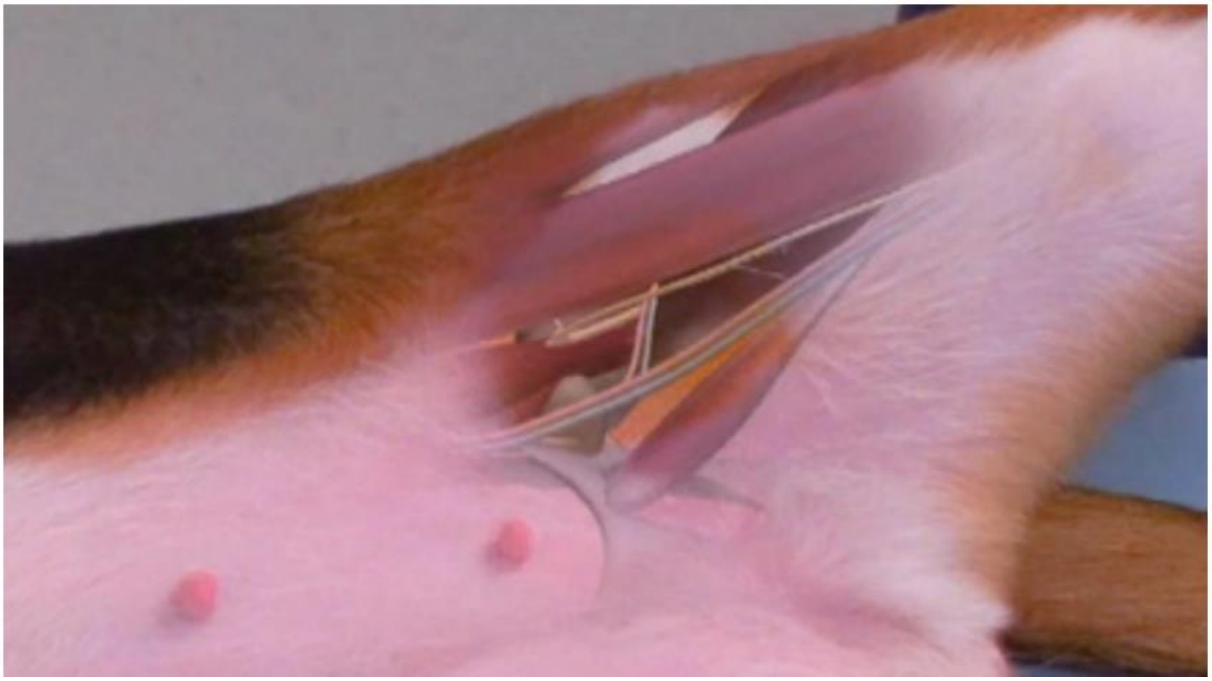


Figure 8. Delimitation of the femoral nerve within the femoral triangle (Campoy and Read, 2013. Small Animal Regional Anesthesia and Analgesia).

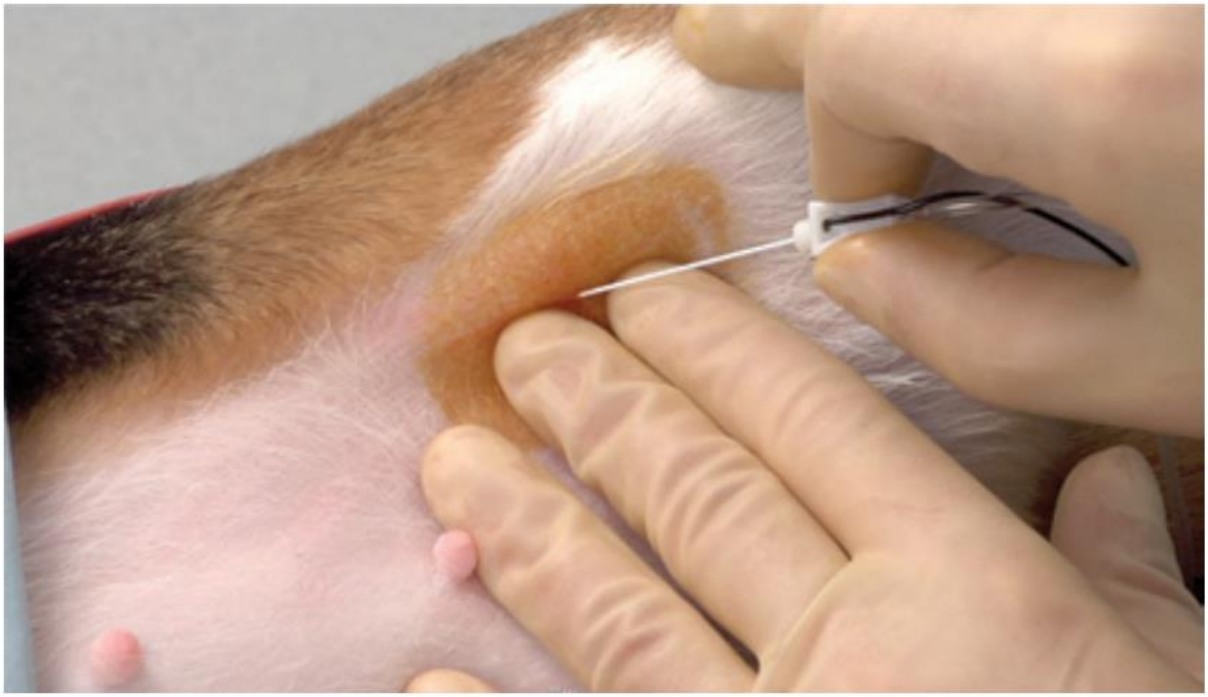


Figure 9. Insertion of the stimulating needle maintaining a 20 – 30-degree angle to the skin in a left sided femoral nerve block (Campoy and Read, 2013. Small Animal Regional Anesthesia and Analgesia).

The femoral block is commonly followed up by a nerve stimulation guided sciatic nerve block and has been described by several authors (Campoy et al., 2008; Mahler and Adogwa, 2008; Portela et al. 2010). Nevertheless, for continuity the lateral approach technique described by Campoy et al. (2008) will be described in this review.

Patient position remains the same side lateral recumbency, but with the uppermost leg in natural position. The area between the greater trochanter and ischiatic tuberosity should be identified, clipped, and prepared aseptically. The greater trochanter and ischiatic tuberosity function as landmarks, where the puncture site lies at one-third of the distance from the greater trochanter to the ischiatic tuberosity (Figure 10). Maintaining an angle of 45 degrees and a nerve stimulator current of 1 mA, the needle is inserted and advanced (Figure 11). When the needle is advanced to the correct depth, a positive contraction response can be seen as dorsiflexion or plantar extension of the foot. Similarly, to the femoral block, the current decreased in increments of 0.2 mA until 0.4 mA, while looking for the same positive response (Campoy and Read, 2013; Duke-Novakovski et al., 2016; Read et al., 2024).

Figure 10. A dog positioned for a sciatic nerve block. The sciatic nerve is located at the line between the greater trochanter and ischiatic tuberosity at a point between the cranial and middle thirds (Campoy and Read, 2013. Small Animal Regional Anesthesia and Analgesia).

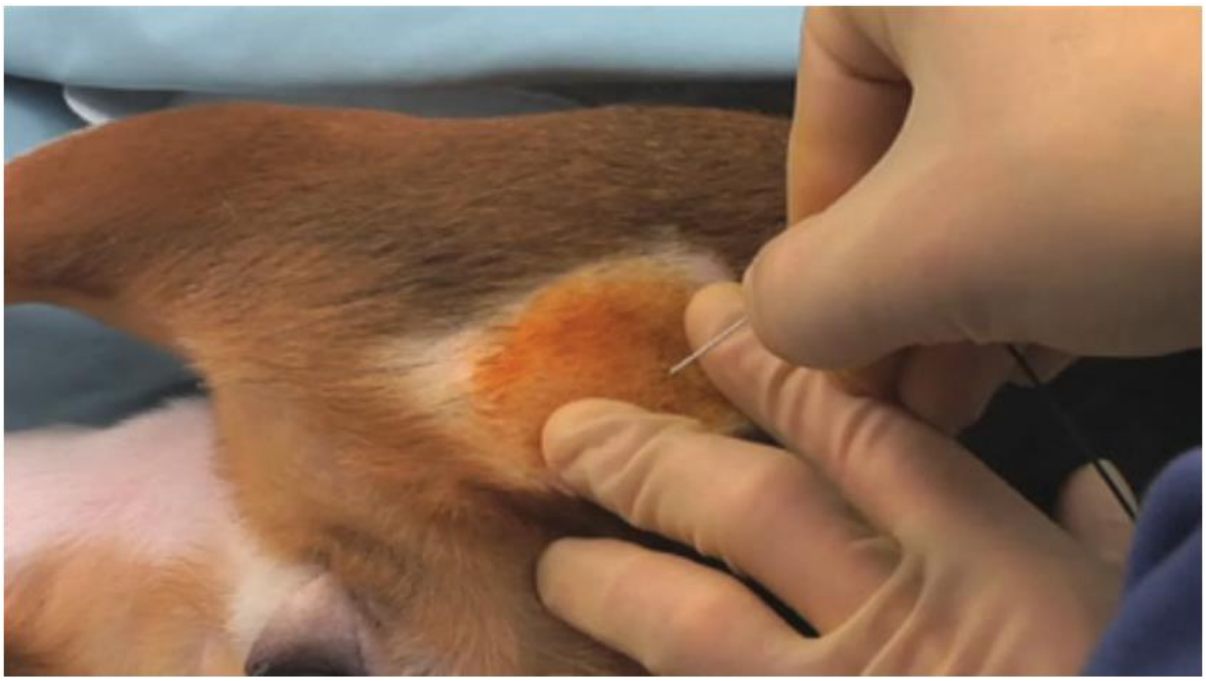


Figure 11. Insertion of the stimulating needle in a left sided sciatic nerve block (Campoy and Read, 2013. Small Animal Regional Anesthesia and Analgesia).

1.4 Epidural anaesthesia

Neuraxial anaesthesia facilitated by epidural use of anaesthetics and analgesic drugs in human as well as veterinary medicine has been routine for decades. As a method of pre-emptive analgesia, the technique aims to decrease central sensitisation, produce muscle relaxation, while also decreasing the requirements for opioids and inhalant agent concentration. Also, as a result, minimising the need for emergency analgesia peri- and postoperatively (Duke-Novakovski et al., 2016; Garcia-Pereira, 2018). Although EPI has become less attractive for clinical research, it retains unique attractive clinical features, such as simple execution, bilateral block, and long-lasting and effective intra- and postoperative analgesia (Sarotti et al. 2022).

In small animals, the main site for EPI injection is into the lumbosacral space outside of the dura, where local anaesthetics produce segmental blockade of lumbar and sacral nerve roots housed within the vertebral canal. Lidocaine and bupivacaine are the most common local anaesthetics for EPI, often combining with morphine to produce a longer lasting analgesic effect (Campoy and Read, 2013; Duke-Novakovski, 2016; Read et al., 2024). Although benefits of the technique often outweigh the risks, possible complications of the technique include contamination, haematoma, respiratory depression, hypotension, bradycardia, neurological deficits, and urinary retention due to inadvertent paralysis of the detrusor muscle (Hansen, 2001; Kona-Boun et al., 2003; Naganobu et al., 2004; Iff and Moens, 2008; Bosmans et al., 2009; Guerrero et al., 2014; Peterson et al., 2014). In a study conducted by Holmberg (2022), as well as in numerous other studies, a decrease in blood pressure can reliably occur due to epidural injection of analgesics. Accidental epidural dose injection into the cerebrospinal fluid (CSF) may also cause complications such as sympathetic blocking, total spinal anaesthesia, or death. Accidental intravenous injection may also lead the patient to receive a toxic dose of local anaesthetic, depending on agent and dose. EPI is also contraindicated when coagulation is impaired, as uncontrolled haematomas may compress neural structures (Martin-Flores, 2019).

1.4.1 Anatomy of epidural space

In dogs, the spinal cord ends at the level of the sixth lumbar vertebra, while the meninges end at the level of the seventh lumbar vertebra. Because of the caudal tapering from the spinal cord and dura at this level, the lumbosacral junction possesses the most space for epidural injection. Within the vertebral column, the meninges and spinal cord are surrounded by the epidural space. Dorsally, the epidural space is limited by the vertebral laminae and the ligamentum flavum (Figure 12).

Communication between epidural and paravertebral space and spinal nerve roots is facilitated by the intervertebral foramina in the lateral walls (Duke-Novakovski et al., 2016; Martin-Flores, 2019). The content inside the epidural space consists of mostly epidural fat, which provides cushion to the spinal cord from impacts (Martin-Flores, 2019).

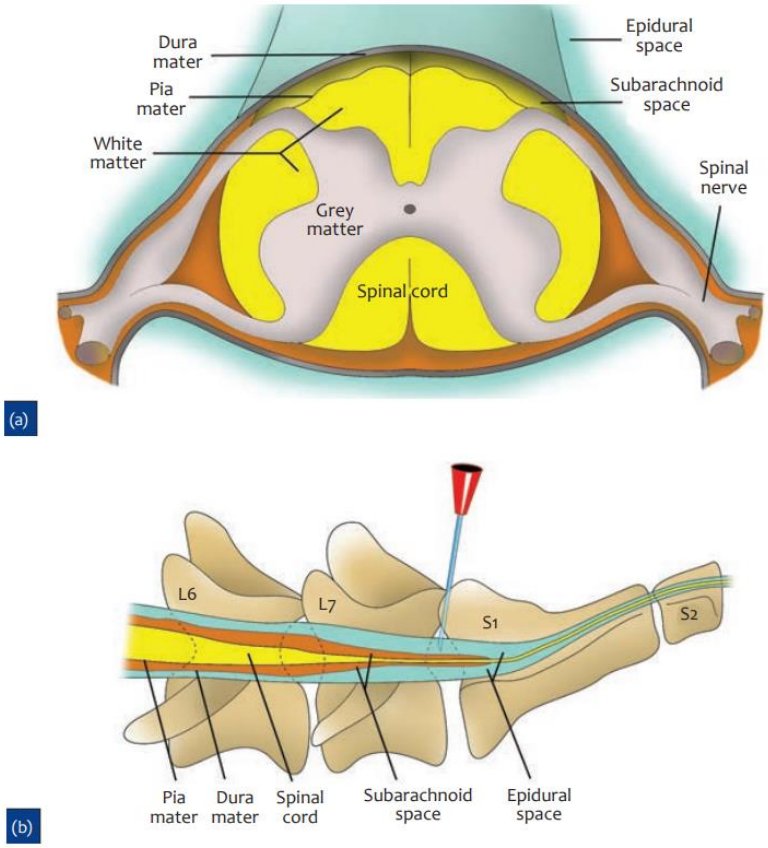


Figure 12. a) Cross-sectional drawing of the epidural space illustrating the divisions between the epidural space and subarachnoid space. b) Cross-sectional drawing in a sagittal view of the lumbosacral area illustrating needle placement into the epidural space. L, Lumbar; S, Sacral (Duke-Novakovski, 2016. BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition).

1.4.2 Techniques

Typically, for routine lumbosacral EPI the patient is placed in either lateral or sternal recumbency, after which the hind limbs can be extended cranially for better access into the lumbosacral junction. The cranial edges of the wings of the ilia should then be palpated and an imaginary line drawn between the points, the lumbosacral junction lies slightly caudal to the line and the indentation between the cranial dorsal spinous process of the seventh lumbar vertebra and caudal sacral ridge should be felt (Figure 13) (Duke-Novakovski et al., 2016).

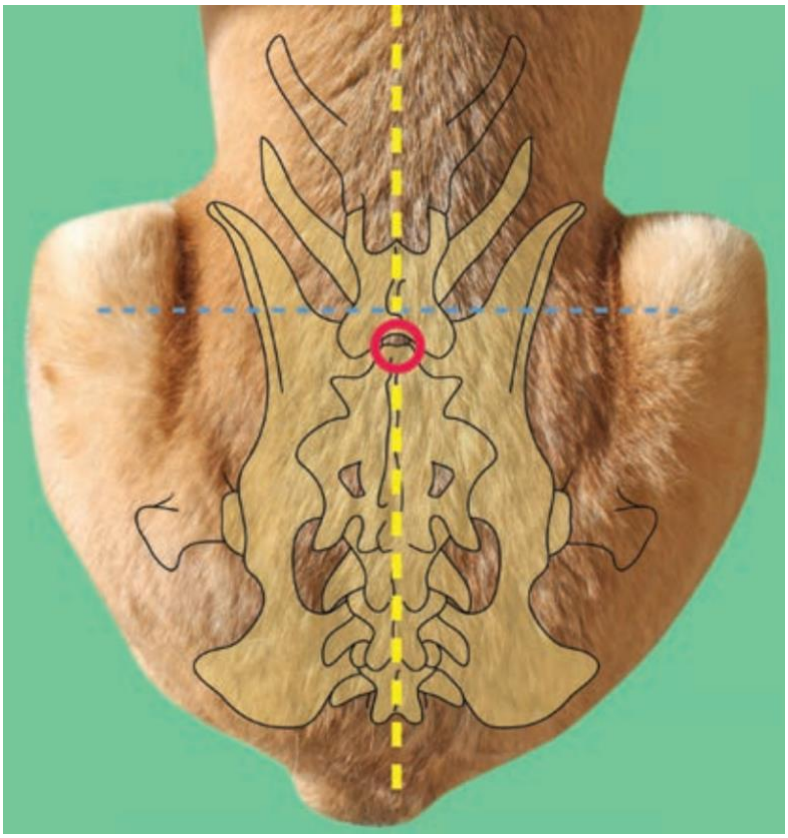


Figure 13. Illustration of the site for a lumbosacral injection. Yellow dashed line designates the vertebral column. Horizontal blue dashed line illustrates the line joining the iliac crests. Injection site indicated by the red circle (Duke-Novakovski, 2016. BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition).

After adequate clipping around the site of injection, aseptic preparation and putting on sterile gloves, a 20-gauge spinal needle is inserted in the centre of the lumbosacral indentation at a 90-degree angle to the plane of the pelvis. The needle is slowly advanced until an increase of resistance is felt followed by sudden 'pop' or loss of the resistance, the ligamentum flavum is now pierced and the needle is positioned in the epidural space. While stabilising the with one hand, the stylet is removed. Although subdural injection is rare, unintentional inward movement of the needle might puncture the collagen fibre rich dura, which is a potential complication due to CSF contact (Martin-Flores, 2019).

Needle placement should thereafter be verified by either a test injection of 1 – 3 ml of air, where an absence of resistance indicates correct needle position, or the 'hanging drop' technique, where a small amount of saline or local anaesthetic is applied into the hub of the needle and the drop can be observed to be pulled in when the needle penetrates the ligamentum flavum due to negative pressure of the epidural space (Figure 14) (Martin-Flores, 2019).

Figure 14. Illustration of the hanging drop technique. Aspiration of the drop indicates entry into the epidural space (Duke-Novakovski, 2016. BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition).

1.5 Mechanism of action of local anaesthetics

Peripheral nociception is facilitated by the myelinated and unmyelinated fibres, which are surrounded by connective tissue sheaths. Local anaesthetics are injected near peripheral nerves and must penetrate these sheaths to reach the neuronal membranes (Duke-Novakovski et al., 2016). Their main objective is to block transmission of nociceptive signals to the CNS by inhibiting impulse conduction at the voltage-gated sodium channels along A-delta and C-fibres. The binding site is located on the cytoplasmic or intracellular surface of the sodium channels (Campoy and Read, 2013; Duke-Novakovski et al., 2016).

The duration and onset of a local anaesthetic blockade is dependent on the drug used, the nerve fibre type, anatomical location of the block, as well as the repetitiveness of noxious stimuli. The ability for a local anaesthetic to block some nerve fibres while sparing others was already first described by Gasser and Erlanger almost a century ago. Now commonly referred to as differential or selective blocking of nerve fibres, meaning that small, myelinated fibres (A-delta) are more susceptible to local anaesthetic blocks than larger diameter proprio- (A-alpha) and mechanoceptors (A-beta) (Campoy and Read, 2013; Read et al., 2024). Although it has been shown that size and myelination is not the be-all and end-all

in terms of selectiveness, there is agreement that A-delta and C-fibres are in general desensitised before proprioceptive A-alpha fibres. Therefore, preferential blocking of noxious stimuli can be achieved with minimal motor block. Essentially meaning, that local anaesthetics aim to block sensitivity and pain before blocking motor function of the affected region, making recovery quicker (Campoy and Read, 2013; Duke-Novakovski et al., 2016; Read et al., 2024).

1.5.1 Lidocaine

Lidocaine has a rapid onset of action of 1 – 2 (up to five) minutes and intermediate duration of action at 60 – 120 minutes (Grubb and Lobprise, 2020). Lidocaine is most used for local anaesthesia of peripheral nerves, neuraxial anaesthesia, local infiltration, intravenous regional anaesthesia and topical desensitisation of skin and mucosa. The drug is also a unique local anaesthetic occasionally used systemically as an intravenous agent, due to its analgesic, anti-inflammatory and antiarrhythmic effects. In dogs, concentrations of 1 – 2% are commonly used in for regional nerve blocks at a dose of 4 – 6 mg/kg (Campoy and Read, 2013; Grubb and Lobprise, 2020; Beecham et al., 2022).

1.5.2 Bupivacaine

Bupivacaine has a slow onset of action compared to lidocaine at 10 – 30 minutes but a much longer duration at 240 – 360 minutes (Lemke and Dawson, 2000; Duke-Novakovski et al., 2016). It is also one of the most common local anaesthetic drugs used for nerve blocks and neuraxial anaesthesia, however bupivacaine is considerably more cardiotoxic than other local anaesthetic agents (Campoy and Read, 2013; Duke-Novakovski et al., 2016). The utilisation of bupivacaine is not as varied as lidocaine, but its longer duration of action makes it a viable choice for peri- and postoperative analgesia. It has been reported that bupivacaine also has good differential blocking abilities, as it produces stronger sensory blockade and minimal motor blockade. Concentrations of bupivacaine range from 0.125 – 0.75% and a dose should not exceed 2 mg/kg in clinically healthy animals, as overdose could result in convulsive activity (Figure 15) (Lemke and Dawson, 2000; Campoy and Read, 2013; Grubb and Lobprise, 2020).

Drug	Time to onset of peak effect (minutes)	Duration of effect (hours)	Toxic dose	Maximum safe dose
Lidocaine	2-5	1-2 with adrenaline <1 no adrenaline	Dog 22 mg/kg IV Cat 11 mg/kg IV	Dog 10 mg/kg Cat 6 mg/kg
Mepivacaine	2-5	~1.5	Dog 20 mg/kg IV	Dog 10 mg/kg
Bupivacaine	5-10	~2	Dog and cat 4 mg/kg IV	Dog and cat 2 mg/kg
Ropivacaine	5-10	~2	Dog 5 mg/kg IV	Dog 3 mg/kg

Figure 15. Table indicating peak onset time and duration of effect, and doses of local anaesthetic drugs in cats and dogs. Duration of action depends on the method of evaluation. (Duke-Novakovski, 2016. BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition).

1.5.3 Epidural use of morphine

The mixing of opioids and local anaesthetics for neuraxial anaesthesia is widely used. In veterinary medicine, the most common epidural opioid today is morphine. Adding morphine into local anaesthesia improves analgesia and lessens unwanted proprioceptor blockade (Campoy and Read, 2013). A study conducted by Almeida et al. (2010) found that combining morphine and lidocaine for EPI in dogs results in prolonged analgesia without affecting the degree of motor blockade. However, it has been noted by Campoy et al. (2012) that epidural morphine may result in urine retention in around 50% of surgical patients. This is due to its action on *mu* receptors in the spinal cord, inhibiting the release of acetylcholine from parasympathetic sacral nerves that control detrusor tone (Peterson et al., 2014). Pre-emptive morphine use prior to anaesthesia may also increase the risk for gastro-oesophageal reflux and may cause emesis and relevant histamine release if given intravenously (IV). Epidural administration of morphine is commonly given at a dose of 0.1 - 0.2 mg/kg in combination with a local anaesthetic agent. Morphine can also be administered as a constant rate infusion (CRI) in order to provide a consistent level of analgesia instead of intermittent boluses, leading to minimising adverse reactions and decreasing overall morphine use (Duke-Novakovski et al., 2016; King and Boag, 2018).

1.6 Emergency analgesia

Rescue- or emergency analgesia is a commonly used term used for analgesic intervention in case of acute pain. Opioids are a frequently used drug class for emergency analgesia due to acute surgical pain, however many opioids are also safely used for sedation, induction, and maintenance of anaesthesia. Opioids provide profound analgesia, while being safe for the cardiovascular system and myocardial

contractility (King and Boag, 2018). However, opioids may cause dose-dependent respiratory depression, which is exacerbated when combined with potent hypnotic drugs like propofol and inhalation agents, or in the case of ill patients (King and Boag, 2018). Both the desirable and undesirable traits of opioids stem from their modulation and activity at opioid receptors within the central nervous system. In general, the higher the lipophilicity the shorter duration of action an opioid has (Duke-Novakovski, 2016). Morphine for example is around ten times longer lasting than fentanyl due to its hydrophilic nature, but fentanyl is one hundred times more potent (Duke-Novakovski, 2016).

Opioid receptors have a large variance in binding properties, functional activity, and distribution within the nervous system. Nonetheless, all opioid receptors are bound to G-proteins and inhibit adenylate cyclase, resulting in the decrease of conduction at voltage-gated calcium channels and inwardly rectifying potassium channels (Duke-Novakovski, 2016). In current literature three major classes of opioid receptors are recognised, *mu*, *delta,* and *kappa*, and all three classes mediate analgesia. The opioid drugs acting on opioid receptors are classified as agonists, partial agonists, mixed agonists, and antagonists. All opioids (morphine, fentanyl, methadone) commonly used for analgesic purposes are full agonists and have a high affinity and intrinsic activity for mu receptors. Mu agonists are recommended in case of moderate to severe pain (Duke-Novakovski et al., 2016).

1.6.1 Fentanyl

Fentanyl is a potent and fast acting synthetic pure mu agonist that can be administered intramuscularly (IM), subcutaneously (SC), transdermally, or IV. Intravenous administration produces a fast onset of action at one to two minutes and a short duration of action of 20 – 30 minutes. When severe acute surgical pain is noted, an intravenous bolus is commonly used at a dose of 5 – 20 µg/kg (Duke-Novakovski et al., 2016). Fentanyl can also be given as a CRI, usually combined with other analgesics for maximum effect, or transdermally as a fentanyl patch to manage postoperative pain. Fentanyl also possesses a high MAC-sparing effect of 40 – 50% during anaesthesia. CRI dose of fentanyl is given as a 3 – 5 µg/kg bolus, followed by 3 – 6 µg/kg/h IV (Duke-Novakovski et al., 2016; King and Boag, 2018).

1.6.2 Methadone

Although not optimal for fast acting intraoperative pain relief, due to its slower onset of action of approximately 10 minutes when administered IV, methadone is an option for emergency analgesia if fentanyl is not available. Administered IM or IV, methadone is a synthetic mu receptor agonist with similar analgesic properties, potency, and duration of action to morphine but possessing a weaker sedative effect. Compared to morphine, which has an affinity to mu receptors and to some degree for kappa and delta receptors, methadone has a higher relative intrinsic efficacy on mu receptors, while in addition having variable affinity to NMDA receptors and alpha-2-adrenergic receptors which aids in suppressing central sensitisation (Ingvast-Larsson et al., 2010; Murrell, 2011). Methadone is also less likely to induce emesis and therefore a more favourable option at induction (Duke-Novakovski et al., 2016). Recommended dose of methadone in dogs is 0.1-0.5 mg/kg IM or IV (Figure 16) (Duke-Novakovski et al., 2016; King and Boag, 2018)

Drug	Classification (potency relative to morphine)	Duration of effect of one bolus (hours)	Dosage forms	Dose
Morphine	Mu agonist (1)	2-6	Injectable: 0.5-50 mg/ml	0.1-1 mg/kg slow IV, IM or SC Infusion: 0.12-0.34 mg/kg/h
Methadone	Mu agonist (1)	4-8	Injectable: 10 mg/ml	0.1-0.5 mg/kg IV, IM or SC
Buprenorphine	Partial mu agonist	4-12	Injectable: 0.3 mg/ml	0.01-0.03 mg/kg IV or IM
Fentanyl	Mu agonist (100)	20-30	Injectable: 50 and 78.5 µg/ml Transdermal patch: 25, 50, 75 and 100 µg/h Transdermal solution: 50 mg/ml	Injectable: 2-5 µg/kg bolus Infusion rate: Intraoperative 5-40 µg/kg/h Postoperative 3-6 µg/kg/h Transdermal 2-5 µg/kg/h

Figure 16. Opioid analgesics routinely used in dogs. (Duke-Novakovski, 2016. BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition).

1.6.3 Ketamine

Ketamine is a safe and commonly used non-competitive anaesthetic drug that targets the NMDA receptor directly and is a useful component of an MMA protocol. Often referred to as a dissociative anaesthetic, ketamine facilitates a characteristic hypnotic trancelike state where eyes remain open and a cataleptic body rigidity can be seen (Duke-Novakovski, 2016; Pardo, 2022). Ketamine has been shown to selectively decrease NMDA receptor activation and reduce neuron activity in humans and animals, resulting in a strong decrease in central sensitisation and peripheral analgesia at the spinal cord, depressing the progressive increase of wind-up (Guirimand et al., 2000; Tsui and Chu, 2017). In

contrast to opioids, ketamine produces potent analgesia with minimal respiratory depression and relative cardiovascular stability when combined with benzodiazepines, opioids, or inhaled anaesthetics. Ketamine has additional proposed functions on opioid receptors and/or activation of noradrenergic and serotonergic receptors that produce analgesic effects (Duke-Novakovski, 2016; Pardo, 2022).

Ketamine has a fast onset of action and half-life of around 30 minutes, thanks to its high lipid solubility (Pardo, 2022). Routes of administration are also versatile (IV, IM, SC, *per os*), IV route being the most common and CRI also being a frequently used option. The recommended dose of ketamine in dogs is 0.2 – 4 mg/kg IV bolus followed by CRI of 5 – 10 µg/kg/minute based on patient response (Duke-Novakovski et al., 2016; Self, 2019; Pardo, 2022).

1.6.4 Fentanyl lidocaine ketamine constant rate infusion

Fentanyl lidocaine ketamine (FLK) constant rate infusion (CRI), to reduce inhalation anaesthetic requirements and provide effective intraoperative analgesia, is increasing in popularity in veterinary medicine and can be an effective tool within the MMA strategy (Aguado et al., 2010; Marques et al., 2023). FLK dilutions are commonly put in a 500 ml 0.9% NaCl bottle, from where an appropriate amount of saline is removed and replaced with an equivalent amount of fentanyl, lidocaine, and ketamine in a predetermined dosage ratio. CRI is started at 1 ml/kg/h, adjusting up or down depending on patient response and pain level.

1.7 Cranial cruciate ligament rupture

Cook (2010) describes the disease simply as joint organ failure, where many factors are interrelated, exacerbate one another, and ultimately lead to pain, dysfunction, and lameness. CCL rupture is the most frequent cause of hind limb meniscal damage, osteoarthritis, and lameness in dogs. Although CCL rupture has been reported to happen due to sudden trauma, the consensus is that in most cases of rupture there is an underlying degenerative issue within the organ (Cook, 2010). For long-term and pain free limb function, all components of the joint must function biologically and biomechanically (Cook, 2010; Binversie et al., 2022).

Currently in good candidates, treatment of CCL rupture is commonly done by surgical procedure, of which tibial osteotomies make up the majority. TPLO and the TTA RAPID are two commonly used surgical techniques, where the latter aims to neutralise cranial tibiofemoral shear force through displacement of the tibial tuberosity cranially to reach a patellar tendon angle of 90 degrees to the tibial plateau (Apelt et al., 2007; Aragosa et al., 2022). Both techniques include a medial arthrotomy and a tibial osteotomy, with either subsequent TPLO plate fixation or a TTA RAPID cage. Due to the invasive nature of both techniques, they are associated with significant intraoperative nociception (Papadopoulos et al., 2022).

As CCL disease is painful, the relief of it should be the main goal in the treatment plan. If left untreated, dogs show degenerative joint changes within weeks and severe changes can be seen in a few months (DeCamp, 2015). Joint pain can be mostly derived from nociceptive mediators produced in association with the inflamed and degraded organ. Therefore, in an optimal long-term treatment plan, surgery, joint lavage, debridement of damaged tissues, anti-inflammatory medication and physiotherapy is often warranted (Cook, 2010).

2. AIMS OF THE STUDY

In this case study, the effect on pain response and physiological parameters in a dog undergoing TTA RAPID surgery after receiving pre-operative femoral nerve block was examined.

The specific aims of this study were:

1. To compare peripheral nerve blocks versus epidural anaesthesia.
2. To identify the possible benefits of peripheral nerve blocks versus epidural anaesthesia.
3. To identify the most painful parts of the surgery.

3. MATERIALS AND METHODS

3.1. Case study

The author wants to preface that the socioeconomic conditions while this study was conducted severely affected the number of available TTA cases during the study period, therefore this study was limited to just one case.

A 61 kg (body condition score 5/9) intact male 8 year and 8 months old Landseer dog presented to the Small animal clinic of Estonian University of Life Sciences for TTA RAPID surgery following cranial cruciate ligament rupture of the left hind leg. The dog was otherwise fit and well and had no relevant medical history, known allergies, or complications with previous anaesthesia, and was therefore classed into American Society of Anaesthesiologists (ASA) physical status 1. For use of data in the study, written informed consent was obtained from the client. The dog was fasted since the night prior to surgery, and the dog had free access to water.

3.2 Medications, doses, and routes of administration

The dog received premedication consisting of intramuscular injection of dexmedetomidine (0.003 mg/kg), butorphanol (0.1 mg/kg). Approximately 30 minutes later, induction was facilitated by intravenous injection of ketamine (2 mg/kg) and propofol (2-4 mg/kg until full effect), and orotracheal intubation was performed.

As suggested by the study conducted by Holmberg (2022), the lidocaine dose was increased to 3 mg/kg. Using the nerve locator (Bbraun Stimuplex HNS 12) to stimulate the femoral nerve, the dog received lidocaine at a concentration of 1%, injecting when the nerve was localised. Campoy technique (Campoy, 2006) with a medial approach was used for the femoral nerve block.

For the femoral block, the patient was placed in lateral recumbency, with the limb to be blocked uppermost. The leg was abducted 90° and extended caudally to gain access to the inguinal area, which was clipped and prepared sterilely for puncture. The femoral triangle was delineated by the pectineus muscle caudally, the sartorius muscle cranially, and the iliopsoas proximally. Thereafter, the femoral artery was located by palpation of the femoral pulse. The targeted femoral nerve runs cranially,

adjacent to the femoral artery and vein, and directly medial to the caudal belly of the sartorius muscle. Once landmarks were identified, the insulated needle (22-gauge, 50 mm) was inserted cranial to the femoral artery and advanced, maintaining a 20 – 30 ° angle towards the iliopsoas muscle. The nerve stimulator was set to deliver an initial current of 1mA. Contractions of the quadriceps muscle indicated that the needle was within an appropriate range from the femoral nerve, and to home in on the nerve, current was decreased at 0.2 mA increments until the threshold current of 0.4 mA while retaining the same contracting response.

The end-tidal isoflurane concentration was titrated at a range between 1.3 – 1.7% to maintain a suitable plane of anaesthesia. If pain response was indicated during surgery according to the predetermined thresholds, a fentanyl bolus (2 µg/kg) was given intravenously.

3.3 Anaesthetic monitoring

Following the administration of the local anaesthetic, the patient was transferred to the operating room and positioned for surgery. During anaesthesia, all routine physiological parameters were registered every five minutes. Baseline parameters were collected before the first incision. Furthermore, the following events were marked along the time axis in the data collection sheet: TB (Time baseline) as the baseline 15-minute period prior to the incision, T1 as the period of first incision and approach to the stifle, T2 as the period of osteotomy, T3 as the period of implant placement, and T4 as the period of wound closure.

Respiratory rate (RR), heart rate (HR), End tidal carbon dioxide (ETCO2), body temperature (BT), non-invasive blood pressure (BP), electrocardiography, and end-tidal isoflurane readings were taken and logged by Midmark Cardell Touch veterinary monitor. Oxygen saturation level was measured via pulse oximetry with a clip probe placed on the tongue. A capnography side-stream probe was attached to the endotracheal tube. Body temperature was measured via an esophageal probe. In addition to physiological parameters, mucous membrane color, capillary refill time, palpebral reflex, eye position and jaw tone was monitored to determine patients' response to anaesthesia.

Pain response intraoperatively was determined by an increased HR and RR, while ruling out other factors as a cause, e.g., hypoxemia, hypercarbia, and hypovolemia. The pain response threshold for the fentanyl bolus was agreed by the anesthesiologist, surgeon, and author to be set at a 20 % heart rate increase over the baseline. HR and RR were validated via auscultation every five minutes or when

a pain response was seen. An increased RR and rise in blood pressure was used to further verify a response to noxious stimulus. A perceived pain response indicated by these variables would indicate central sensitisation and failure to prevent nociceptive impulse transmission, and therefore analgesic insufficiency by the local anaesthetics.

3.4 Surgery

Following induction, the patients' surgical site was clipped of hair and the skin antiseptically prepared for surgery. TTA RAPID was successfully performed on the patient without complications. The surgical plan was made with the help of pre-operative radiographs. Postoperative radiographs assessed the osteotomy and implant positioning. Surgery was performed by a medial approach with the patient in lateral recumbency. A suitable implant was chosen, inserted, and fastened with cortical screws. The incision was closed in a routine manner. The urinary bladder was emptied before recovery by caudal compression of the abdomen. The dog was mildly hypothermic throughout the surgery (BT mean ± SD 37.0 ± 0.1), however the body temperature was stable. At the end of the surgery, general anaesthesia was discontinued, and the patient was moved to a quiet recovery area following tracheal extubation. The dog recovered from anaesthesia without complications.

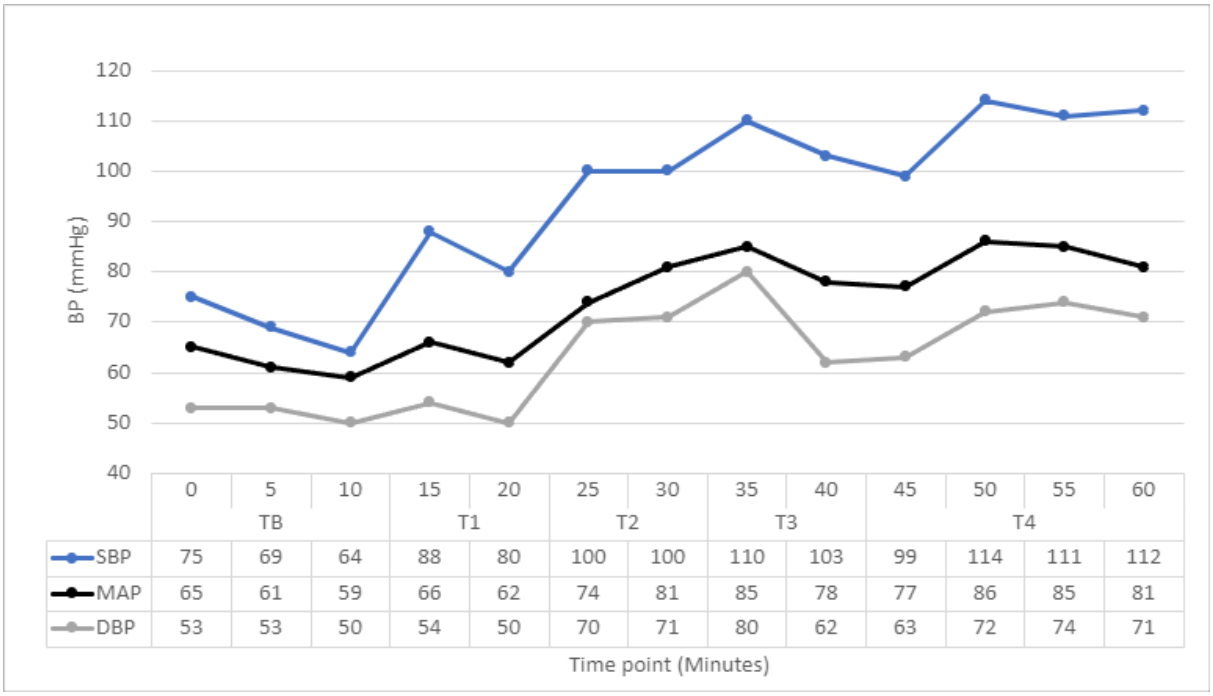
3.5 Statistical analysis

HR, RR, mean arterial blood pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), and number of fentanyl boluses used, were monitored during the procedures, and used as variables in linear regression models. Perceived painful events during surgery were also tracked for when analgesia was inadequate. The mean value was used as the outcome variable for the T1 period.

4. RESULTS

Data from one dog was used in this study. The dog received a dose of lidocaine (3 mg/kg) as a femoral nerve block. The anaesthesia and surgery went without complications.

The total number of fentanyl boluses needed to provide adequate antinociception for the patient was one. A pain reaction was first seen at the osteotomy period (T2) as an increase in HR (TB mean ± SD 71 ± 1 beats/min versus T2 98 beats/min) and MAP (TB mean ± SD 62 ± 3 mmHg versus T2 81 mmHg) over the baseline, and emergency analgesia was provided (Figure 17 and Figure 18). The effect of the fentanyl bolus was seen in the period of implant placement (T3) as a decrease in HR (80 beats/min at the time of measurement) and MAP (78 mmHg at the time of measurement) (Figure 17 and Figure 18). No further fentanyl boluses were deemed necessary during the surgery. BP remained within an acceptable range throughout the procedure. Respiratory rate remained stable throughout the surgery. Emergency analgesia seemed to have no marked effect on respiration (Figure 19). RR varied from 9 to 15 breaths per minute.



	0	5	10	15	20	25	30	35	40	45	50	55	60
	TB			T1		T2		T3		T4			
SBP	75	69	64	88	80	100	100	110	103	99	114	111	112
MAP	65	61	59	66	62	74	81	85	78	77	86	85	81
DBP	53	53	50	54	50	70	71	80	62	63	72	74	71

Figure 17. Intraoperative blood pressure (BP) in a dog undergoing orthopaedic surgery with femoral nerve block. Systolic blood pressure (SBP); Mean arterial blood pressure (MAP); Diastolic blood pressure (DBP); Tb = 15 minutes before the beginning of the surgical procedure; T1 = Period of first skin incision and approach to the stifle; T2 = Period of osteotomy; T3 = Period of implant placement; T4; Period of wound closure.

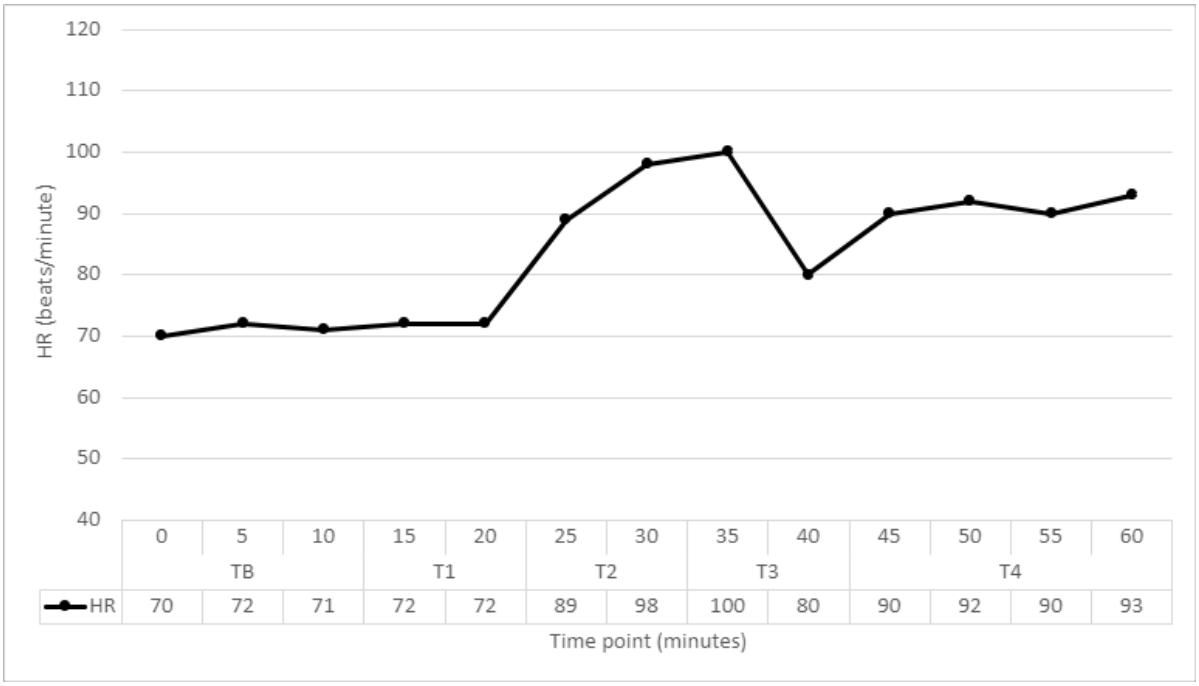


Figure 18. Intraoperative heart rate (HR) in a dog undergoing orthopaedic surgery with femoral nerve block. Tb = 15 minutes before the beginning of the surgical procedure; T1 = Period of skin incision and approach; T2 = Period of osteotomy; T3 = Period of implant placement; T4; Period of wound closure.

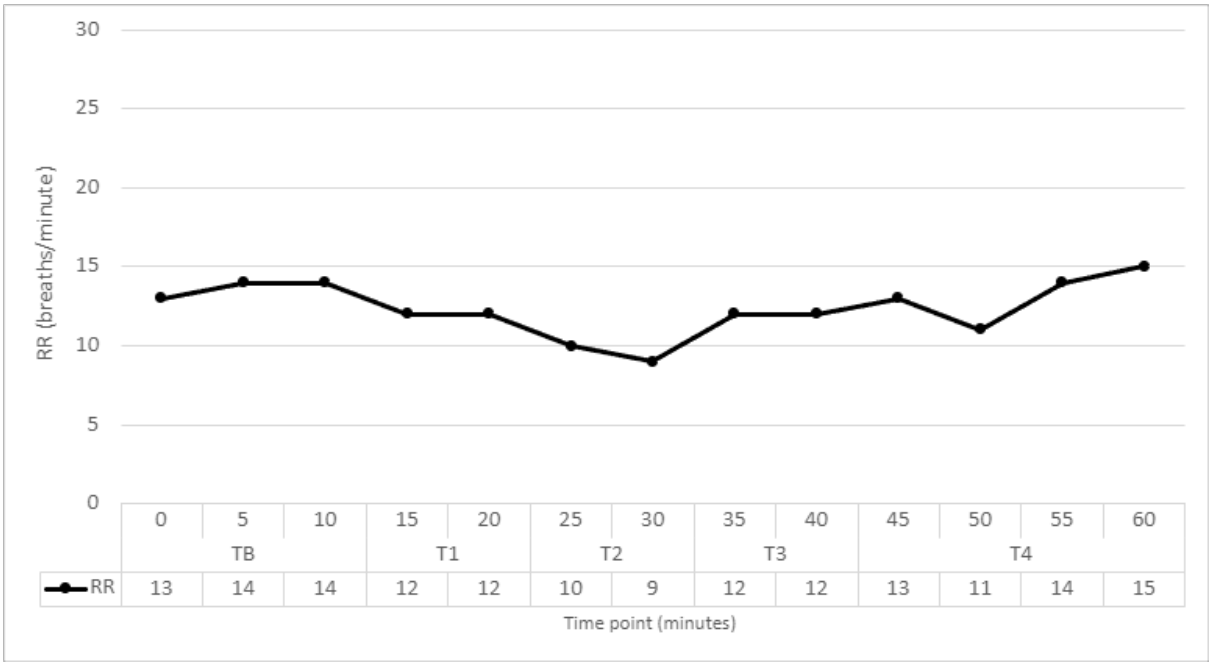


Figure 19. Intraoperative respiratory rate (RR) in a dog undergoing orthopaedic surgery with femoral nerve block. Tb = 15 minutes before the beginning of the surgical procedure; T1 = Period of skin incision and approach; T2 = Period of osteotomy; T3 = Period of implant placement; T4; Period of wound closure.

5. DISCUSSION

Like the findings of Holmberg (2022), where the effect of EPI on pain response during TTA RAPID surgery was evaluated, osteotomy was deemed the most painful part of the surgery and was when emergency analgesia was commonly needed. Nociception was seen similarly during the period osteotomy in the present femoral nerve block patient by an increase in HR and BP (Figure 14 and Figure 15). While arguments can be made that the block was successful by only requiring minor intervention by a single fentanyl bolus, the question still stands of possible analgesic inadequacy of just a single nerve block during invasive procedures involving the stifle. However, it is impossible to say whether the reason for block failure is due to involvement of another nerve in the stifle, or is it a function of dog size, or a combination of these factors, as Papadopoulos et al. (2022) found, dogs >34 kg have shown a higher chance for block failure. Additionally, the chronicity of the joint lesion and therefore possible central sensitisation could not be determined, which could also play a role in nociception as the dog was older and a chronic condition is likely. During the TB period, this patient had a MAP on the lower end of the range for adequate perfusion (62 ± 3 mmHg), this was corrected with an increase to two times maintenance fluid rate. Although deemed necessary for patient safety, this increase would influence later BP measurements. Future studies should strive to have fixed fluid and gas consumption rates as to have a more standardised protocol for a larger sample size.

The innervation of the stifle is complex and composes of numerous larger nerves, and as a result the hot topic in the world of analgesia is to find the optimal combination of nerves as well as drug combinations (Caniglia et al., 2012). For lumbosacral EPI, combining two synergistically acting local anaesthetics has been found to be worthwhile. Cruz et al. (1997) study was the first to demonstrate that a combination of lidocaine and bupivacaine produced longer duration of analgesia, compared with lidocaine alone, and better muscle relaxation, compared with bupivacaine alone. Similarly, Caniglia et al. (2012) found that perineural administration of a lidocaine and bupivacaine mixture at lower than commonly used concentrations offer important advantages over single administration of higher concentrations of bupivacaine, such as avoiding long-lasting motor function impairment and a decreased risk of CNS and cardiac toxic effects. Which furthermore is of particular value as human studies have shown evidence that the size of the local anaesthetic solution volume administered plays a significant role in the success of PNB techniques. Taboada et al. (2006) found that in human patients a larger volume of local anesthetic was necessary for blockade of the sciatic nerve at a more distal site as compared with a more proximal injection site, to the authors knowledge similar studies in animals have not yet been extensively conducted. Nevertheless, this would further support the increase of lidocaine dose in the present study, in lieu of the dose used by Holmberg (2022).

It is known from prior studies that PNB are a practical alternative to EPI, in that PNB produce less urine retention, may reduce opioid consumption in the 24 hours after surgery, and may reduce physiological complications caused by systemic drugs. While EPI might be associated with a lower isoflurane requirement and superior intraoperative analgesia, but lower blood pressure overall (Campoy et al., 2012; Caniglia et al., 2012; Boscan and Wennogle, 2016; Ferrero et al., 2021). Additionally, compared with EPI, reports in human patients undergoing major knee surgery have seen the incidence of postoperative nausea and vomiting to be less with PNB techniques. Although similar findings have yet to be noticed in animals (Caniglia et al., 2012). In the study conducted Holmberg (2022), hypotension was observed in the EPI patients, in contrast, no anaesthetic complications were seen in this PNB patient.

The author's aim was to explore the feasibility and effectiveness of a single femoral nerve block as an alternative to EPI in an MMA protocol. Studies in dogs comparing PNB and EPI largely have a focus on the combination of sciatic and femoral blocks, while a femoral nerve block alone is commonly used in people undergoing knee surgery. Whether a femoral nerve block alone can provide sufficient analgesia for TTA surgery is still unknown (McCally et al., 2015). Comparing to the previous study conducted by Holmberg (2022), suggestions could be made that a simple femoral PNB has a possibility for intraoperative analgesia similar in performance to EPI, without the complications that the analgesic modality has risk of eliciting, although, direct comparison cannot be made as the patients received morphine in addition to lidocaine epidurally. Furthermore, as osteotomy has been established to reliably elicit a strong nociceptive response, the author wants to suggest that it could be worthwhile to add a pre-emptive analgesic bolus before osteotomy, to be part of the standard MMA protocol in orthopaedic surgery, as this could mitigate acute and postoperative pain levels. Further study on pre-emptive analgesia preceding known painful orthopaedic procedures is therefore recommended.

Within recent times as research has shifted away from EPI. PNB have gained favour by animal and human anaesthesiologists alike for good reason. Balancing analgesia and the risk of complications remains an important topic of discussion. It is especially important during invasive orthopaedic surgery, which is prone to be painful, and where postoperative complications due to anaesthesia are undesirable and can affect patient outcome. The review aimed to provide a comprehensive exploration of the current literature surrounding regional anaesthesia, however given the constraints, the reality is that the author was just able to scratch the surface. Ultimately it is known that stifle geometry altering surgeries are especially prone to be painful and perioperative pain can be effectively managed with effective MMA protocols. Studies have shown that PNB in various regions and techniques are

effective at providing perioperative analgesia and perhaps given wider adoption in the future, PNB could replace EPI as the standard protocol in hind limb surgery.

As an ending note, this study was limited by its sample size of TTA patients available at the time of conducting this study, the findings should be taken more as a proof of concept/pilot study for further research rather than actual evidence. Future research with reliable postoperative evaluation, including reflexes, muscle function and skin sensitivity, is also recommended to objectively compare EPI versus femoral PNB.

CONCLUSIONS

The aim of this study was to compare peripheral nerve blocks versus epidural anaesthesia. The findings of this study provide a run-through of a patient that received a successful single femoral nerve block. And as seen, PNB can be excellent at providing perioperative analgesia to the hind limb, while being simple to perform for any surgeon or anaesthesiologist and should be considered as a safe and viable alternative to EPI. Both techniques will reduce the anaesthetic requirement, however if a clinician is reluctant to use opioids epidurally due to its possible complications, a more peripheral approach to analgesia with local anaesthetics may be as effective at providing analgesia as EPI, while lowering the risk for complications. Although regarded as a successful block, some nociception was still seen in the patient leading to administering of a single bolus of emergency analgesia. This could mean that perhaps another block could be beneficial for full blockage of the branches innervating the stifle of a dog.

The study also aimed at identifying possible benefits of the technique by having a deeper look into a patient undergoing TTA RAPID surgery after receiving a pre-emptive nerve block prior to surgery. The main difference to the EPI focused study conducted by Holmberg (2022), was that no hypotension was seen in this patient, which is a known adverse effect of EPI. Concluding that a possible benefit of PNB is a more hemodynamically stable patient.

Additionally, the study aimed to identify the most painful parts of the surgery. And similarly to Holmberg (2022), further supportive evidence was seen of osteotomy being the most painful phase during surgery. This led the author to suggest that perhaps administering a pre-emptive analgesic bolus prior to osteotomy, could be beneficial for the patient and a worthwhile addition to the standard MMA protocol.

Although this study was unsuccessful at its original goal of comprehensively comparing EPI versus PNB due to scarcity of patients, the author would suggest that this study opens up an avenue for future research into pre-emptive analgesia and PNB.

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REFERENCES

AAHA/AAFP Pain Management Guidelines Task Force Members, Hellyer, P., Rodan, I., Brunt, J., Downing, R., Hagedorn, J.E. and Robertson, S.A., 2007. AAHA/AAFP pain management guidelines for dogs and cats. *Journal of feline medicine and surgery*, *9*(6), 466-480.

Aguado, D., Benito, J. and de Segura, I.A.G., 2011. Reduction of the minimum alveolar concentration of isoflurane in dogs using a constant rate of infusion of lidocaine–ketamine in combination with either morphine or fentanyl. *The Veterinary Journal*, 189(1), 63-66.

Almeida, R.M., Escobar, A. and Maguilnik, S., 2010. Comparison of analgesia provided by lidocaine, lidocaine-morphine or lidocaine-tramadol delivered epidurally in dogs following orchiectomy. *Veterinary anaesthesia and analgesia*, 37(6), 542-549.

American Society of Anesthesiologists Task Force on Chronic Pain Management, 2010. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology*, 112(4), 810-833.

Apelt, D., Kowaleski, M.P. and Boudrieau, R.J., 2007. Effect of tibial tuberosity advancement on cranial tibial subluxation in canine cranial cruciate-deficient stifle joints: an in vitro experimental study. *Veterinary Surgery*, 36(2), 170-177.

Aragosa, F., Caterino, C., Della Valle, G. and Fatone, G., 2022. Tibial tuberosity advancement techniques (TTAT): a systematic review. *Animals*, 12(16), 2114.

Basbaum, A.I., Bautista, D.M., Scherrer, G. and Julius, D., 2009. Cellular and molecular mechanisms of pain. *Cell*, 139(2), 267-284.

Beecham, G.B., Nessel, T.A. and Goyal, A., 2022. Lidocaine. StatPearls. Treasure Island (FL).

Binversie, E.E., Walczak, B.E., Cone, S.G., Baker, L.A., Scerpella, T.A. and Muir, P., 2022. Canine ACL rupture: a spontaneous large animal model of human ACL rupture. *BMC Musculoskeletal Disorders*, 23(1), 1-12.

Boscan, P. and Wennogle, S., 2016. Evaluating femoral-sciatic nerve blocks, epidural analgesia, and no use of regional analgesia in dogs undergoing tibia-plateau-leveling-osteotomy. *Journal of the American Animal Hospital Association*, 52(2), 102-108.

Bosmans, T., Schauvliege, S., Gasthuys, F., Marcilla, M.G. and Polis, I., 2009. Transient unilateral Horner's syndrome after epidural ropivacaine in a dog. *Veterinary anaesthesia and analgesia*, 36(4), 401-406.

Brennan, F., Carr, D. B., & Cousins, M. (2007). Pain management: a fundamental human right. *Anesthesia & Analgesia*, 105(1), 205-221.

Campoy L and Read M (2013) Small Animal Regional Anaesthesia, 1st edn. John Wiley & Sons.

Campoy, L., 2008. Fundamentals of regional anesthesia using nerve stimulation in the dog. Recent advances in veterinary anesthesia and analgesia: companion animals. Gleed RD and Ludders JW (eds). Ithaca NY International Veterinary Information Service.

Campoy, L., Martin-Flores, M., Ludders, J.W., Erb, H.N. and Gleed, R.D., 2012. Comparison of bupivacaine femoral and sciatic nerve block versus bupivacaine and morphine epidural for stifle surgery in dogs. *Veterinary Anaesthesia and Analgesia*, 39(1), 91-98.

Chen, J.S., Kandle, P.F., Murray, I., Fitzgerald, L.A. and Sehdev, J.S., 2019. Physiology, pain. StatPearls Publishing.

Caniglia, A.M., Driessen, B., Puerto, D.A., Bretz, B., Boston, R.C. and Larenza, M.P., 2012. Intraoperative antinociception and postoperative analgesia following epidural anesthesia versus femoral and sciatic nerve blockade in dogs undergoing stifle joint surgery. *Journal of the American Veterinary Medical Association*, 241(12), 1605-1612.

Cook, J.L., 2010. Cranial cruciate ligament disease in dogs: biology versus biomechanics. *Veterinary Surgery*, 39(3), 270-277.

Cruz, M.L., Luna, S.P.L., Clark, R.M.O., Massone, F. and Castro, G.B., 1997. Epidural anaesthesia using lignocaine, bupivacaine or a mixture of lignocaine and bupivacaine in dogs. *Journal of veterinary anaesthesia*, 24(1), 30-32.

DeCamp, C.E., 2015. Brinker, Piermattei and Flo's handbook of small animal orthopedics and fracture repair. *Elsevier Health Sciences*.

Di Franco, C., Cipollini, C., Figà Talamanca, G., Tazioli, G., Patroncini, S., Calistri, M. and Briganti, A., 2023. Saphenous and Sciatic Nerve Blockade with and without Obturator Nerve Block for Tibial Plateau Levelling Osteotomy Surgery in Dogs: A Randomized Controlled Trial. *Animals*, 13(24), 3792.

Dillane, D. and Tsui, B.C., 2012. Is there still a place for the use of nerve stimulation?. *Pediatric Anesthesia*, *22*(1), 102-108.

Dugdale, A.H., Beaumont, G., Bradbrook, C. and Gurney, M., 2020. Veterinary anaesthesia: principles to practice. John Wiley & Sons.

Duke-Novakovski, T., Vries, M.D. and Seymour, C., 2016. BSAVA manual of canine and feline anaesthesia and analgesia (No. Ed. 3). *British Small Animal Veterinary Association*.

Ferrero, C., Borland, K. and Rioja, E., 2021. Retrospective comparison of three locoregional techniques for pelvic limb surgery in dogs. *Veterinary Anaesthesia and Analgesia*, 48(4), 554-562.

Garcia-Pereira, F., 2018. Epidural anesthesia and analgesia in small animal practice: an update. *The Veterinary Journal*, 242, 24-32.

Gasser, H.S. and Erlanger, J., 1929. The role of fiber size in the establishment of a nerve block by pressure or cocaine. *American Journal of Physiology-Legacy Content*, 88(4), 581-591.

Gentili, M.E. and Wargnier, J.P., 1993. Peripheral-nerve damage and regional anesthesia. *British journal of anaesthesia*, *70*(5), 595-595.

Greenblatt, G. M., & Denson, J. S. (1962). Needle nerve stimulator-locator: nerve blocks with a new instrument for locating nerves. *Anesthesia & Analgesia*, 41(5), 599-602.

Grubb, T. and Lobprise, H., 2020. Local and regional anaesthesia in dogs and cats: Overview of concepts and drugs (Part 1). *Veterinary medicine and science*, 6(2), 209-217.

Gruen, M.E., Lascelles, B.D.X., Colleran, E., Gottlieb, A., Johnson, J., Lotsikas, P., Marcellin-Little, D. and Wright, B., 2022. 2022 AAHA pain management guidelines for dogs and cats. *Journal of the American Animal Hospital Association*, 58(2), 55-76.

Gruen, M.E., White, P. and Hare, B., 2020. Do dog breeds differ in pain sensitivity? Veterinarians and the public believe they do. *PLoS One*, *15*(3), e0230315.

Guerrero, K.K., Guerrero, T.G., Schweizer-Kölliker, M., Ringer, S.K., Hässig, M. and Bettschart-Wolfensberger, R., 2014. Incidence of delayed hair re-growth, pruritus, and urinary retention after epidural anaesthesia in dogs. *Tierärztliche Praxis Ausgabe K: Kleintiere/Heimtiere*, 42(02), 94-100.

Guirimand, F., Dupont, X., Brasseur, L., Chauvin, M., & Bouhassira, D., 2000. The effects of ketamine on the temporal summation (wind-up) of the R(III) nociceptive flexion reflex and pain in humans. *Anesthesia and analgesia*, 90(2), 408–414.

Hadzic, A. ed., 2017. Hadzic's textbook of regional anesthesia and acute pain management. New York: McGraw-Hill Education. 568-573.

Hansen, B.D., 2001. Epidural catheter analgesia in dogs and cats: technique and review of 182 cases (1991–1999). *Journal of veterinary emergency and critical care*, 11(2), 95-103.

Holmberg, C.S., 2022. Effect of epidural anaesthesia to pain response during tibial tuberosity advancement rapid surgery in dogs. Thesis for Master's degree, Tartu.

Iff, I. and Moens, Y., 2008. Two cases of bradyarrhythmia and hypotension after extradural injections in dogs. *Veterinary anaesthesia and analgesia*, 35(3), 265-269.

Ingvast-Larsson, C., Holgersson, A., Bondesson, U., Lagerstedt, A.S. and Olsson, K., 2010. Clinical pharmacology of methadone in dogs. *Veterinary Anaesthesia and Analgesia*, 37(1), 48-56.

King, L.G. and Boag, A., 2018. BSAVA manual of canine and feline emergency and critical care (No. Ed. 3). *British small animal veterinary association*.

Kona–Boun, J.J., Pibarot, P. and Quesnel, A., 2003. Myoclonus and urinary retention following subarachnoid morphine injection in a dog. *Veterinary Anaesthesia and Analgesia*, 30(4), 257-264.

Lamont, L.A., 2008. Multimodal pain management in veterinary medicine: the physiologic basis of pharmacologic therapies. *Veterinary Clinics of North America: Small Animal Practice*, 38(6), 1173-1186.

Lemke, K.A. and Dawson, S.D., 2000. Local and regional anesthesia. *Veterinary Clinics: Small Animal Practice*, 30(4), 839-857.

Mahler, S.P. and Adogwa, A.O., 2008. Anatomical and experimental studies of brachial plexus, sciatic, and femoral nerve-location using peripheral nerve stimulation in the dog. *Veterinary anaesthesia and analgesia*, 35(1), 80-89.

Martin-Flores, M., 2019. Epidural and spinal anesthesia. *Veterinary Clinics: Small Animal Practice*, 49(6), 1095-1108.

Mathews, K., Kronen, P.W., Lascelles, D., Nolan, A., Robertson, S., Steagall, P.V., Wright, B. and Yamashita, K., 2014. Guidelines for recognition, assessment and treatment of pain: WSAVA Global Pain Council members and co-authors of this document. *Journal of Small Animal Practice*, *55*(6).

Marques, É.J., Monteiro, E.R., Herrera-Becerra, J.R., Tomazeli, D., Rovaris, I.B., de Oliveira, T.F., Valle, S.D.F. and Alievi, M.M., 2023. Influence of Constant Rate Infusions of Fentanyl Alone or in Combination

with Lidocaine and Ketamine on the Response to Surgery and Postoperative Pain in Isoflurane Anesthetized Dogs Undergoing Unilateral Mastectomy: A Randomized Clinical Trial. *Topics in Companion Animal Medicine*, 52, 100-759.

McCally, R.E., Bukoski, A., Branson, K.R., Fox, D.B. and Cook, J.L., 2015. Comparison of short-term postoperative analgesia by epidural, femoral nerve block, or combination femoral and sciatic nerve block in dogs undergoing Tibial Plateau leveling osteotomy. *Veterinary Surgery*, 44(8), 983-987.

Murrell, J., 2011. Clinical use of methadone in cats and dogs. *UK Vet Companion Animal*, 16(5), 56-61.

Naganobu, K., Maeda, N., Miyamoto, T., Hagio, M., Nakamura, T. and Takasaki, M., 2004. Cardiorespiratory effects of epidural administration of morphine and fentanyl in dogs anesthetized with sevoflurane. *Journal of the American Veterinary Medical Association*, 224(1), 67-70.

Pardo, M. ed., 2022. Miller's basics of anesthesia. *Elsevier Health Sciences*.

Parker, L.A., Bukoski, A.D., Zelaya-Nunez, C., Dodam, J.R., Varner, K.M. and Torres, B.T., 2023. Pelvic limb anesthesia and analgesia in dogs undergoing tibial plateau leveling osteotomy (TPLO): A survey of board-certified anesthesiologists. *Veterinary Surgery*, 52(4), 521-530.

Peterson, N. W., Buote, N. J., & Bergman, P. (2014). Effect of epidural analgesia with opioids on the prevalence of urinary retention in dogs undergoing surgery for cranial cruciate ligament rupture. *Journal of the American Veterinary Medical Association*, 244(8), 940-943.

Portela, D.A., Otero, P.E., Briganti, A., Romano, M., Corletto, F. and Breghi, G., 2013. Femoral nerve block: a novel psoas compartment lateral pre-iliac approach in dogs. *Veterinary anaesthesia and analgesia*, 40(2), 194-204.

Portela, D.A., Otero, P.E., Tarragona, L., Briganti, A., Breghi, G. and Melanie, P., 2010. Combined paravertebral plexus block and parasacral sciatic block in healthy dogs. *Veterinary anaesthesia and analgesia*, 37(6), 531-541.

Portela, D.A., Verdier, N. and Otero, P.E., 2018. Regional anesthetic techniques for the thoracic limb and thorax in small animals: A review of the literature and technique description. *The Veterinary Journal*, *241*, 8-19.

Papadopoulos, G., Duckwitz, V. and Doherr, M.G., 2022. Femoral and sciatic nerve blockade of the pelvic limb with and without obturator nerve block for tibial plateau levelling osteotomy surgery in dogs. *Veterinary Anaesthesia and Analgesia*, 49(4), 407-416.

Raja, S.N., Carr, D.B., Cohen, M., Finnerup, N.B., Flor, H., Gibson, S., Keefe, F.J., Mogil, J.S., Ringkamp, M., Sluka, K.A. and Song, X.J., 2020. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*, 161(9), 1976-1982.

Read, M.R., Campoy, L. and Fischer, B. eds., 2024. Small animal regional anesthesia and analgesia. John Wiley & Sons.

Sarotti, D., Ala, U. and Franci, P., 2022. Epidural anesthesia in dogs undergoing hindlimb orthopedic surgery: effects of two injection sites. *Journal of Veterinary Medical Science*, 84(3), 457-464.

Schwenk, E.S. and Mariano, E.R., 2018. Designing the ideal perioperative pain management plan starts with multimodal analgesia. *Korean Journal of Anesthesiology*, 71(5), 345-352.

Self, I., 2019. BSAVA guide to pain management in small animal practice. *British Small Animal Veterinary Association*.

Taboada, M., Rodríguez, J., Valino, C., Carceller, J., Bascuas, B., Oliveira, J., Alvarez, J., Gude, F. and Atanassoff, P.G., 2006. What is the minimum effective volume of local anesthetic required for sciatic nerve blockade? A prospective, randomized comparison between a popliteal and a subgluteal approach. *Anesthesia & Analgesia*, 102(2), 593-597.

Tsui, P.Y. and Chu, M.C., 2017. Ketamine: an old drug revitalized in pain medicine. *BJA Education*, 17(3), 84-87.

APPENDICES

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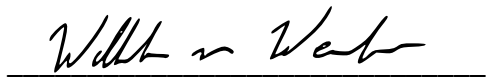
Author of the final thesis 
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