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COMBINATION OF MAGNESIUM SULPHATE AND ROPIVACAINE FOR LUMBO-SACRAL EPIDURAL ANALGESIA IN DOGS UNDERGOING HIP ARTHROPLASTY: AN INVESTIGATOR-BLIND, RANDOMIZED, PROSPECTIVE CLINICAL TRIAL.

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To my family

ACKNOWLEDGEMENTS

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Elena Lardone

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INTRODUCTION

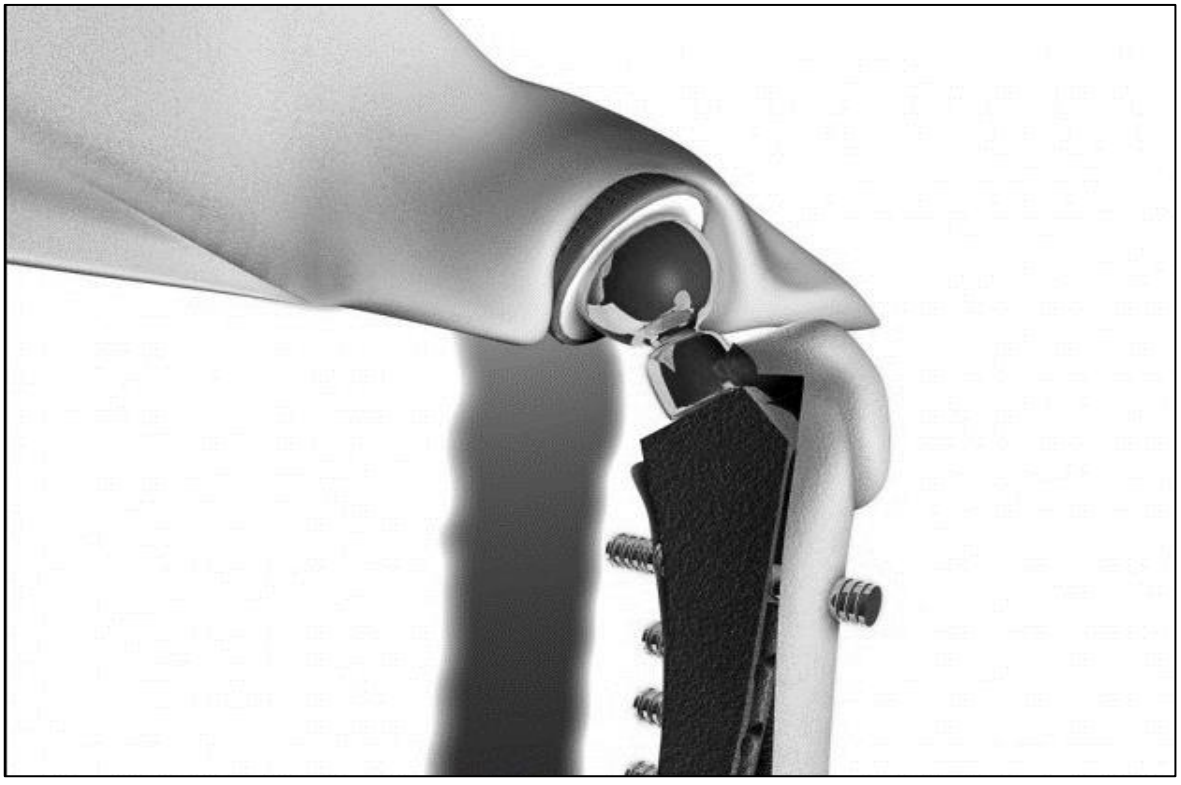
TOTAL HIP REPLACEMENT (THR)

Canine hip dysplasia (CHD) is a common condition, especially in larger breeds, and is characterized by a poor fit of the femoral head in the acetabulum. This poor fit is a result of looseness or laxity in the hip, which leads to pain, osteoarthritis, and decreased limb function. Many factors can contribute to the development of CHD, but genetics is by far the most significant one.

Total hip replacement (THR) is an innovative and complicated procedure used in dogs to treat hip dysplasia and other pathological conditions affecting the coxofemoral joint. In the last decade this technique has gained wide popularity and is now routinarily performed in many specialized surgical centres. It has been shown to be a highly successful method of restoring normal, pain-free motion to the hip (Olmstead, 1987).

Hip arthroplasty involves moderate soft tissue elevation, arthrotomy, femoral head osteotomy, and prosthesis application. As THR is an invasive technique, dogs undergoing this kind of surgery may experience severe pain in the peri-operative period (Fig.1).

Figure 1. *Total hip replacement.*



PERIOPERATIVE ANALGESIA

Providing adequate perioperative analgesia during invasive orthopaedic surgeries not only is an ethical obligation for the veterinarian, but also plays a crucial role in the outcome of the surgery itself (Conzemius et al. 2005). Indeed, effective prevention and treatment of pain has been shown to significantly improve patient's attitude, as well as limb's use and function (Conzemius et al. 2005).

Physiology of pain

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 (Merskey 1979; Bonica 1990; Chaplan and Sorkin 1997). Thus, pain is an experience involving both a physiologic sensation and an emotional or, as is the case for nonverbal animals, behavioural reaction to that sensation. The development of rational and effective pain management strategies requires a basic understanding of pain physiology in order not only to easily anticipate and recognize pain but also to better use pharmacologic agents.

Physiologic pain

The pain that occurs after most types of noxious stimulation is termed physiologic pain (Fig.2). This kind of pain is usually protective and is a part of the body's normal defense mechanisms. It is also often referred to as nociceptive pain because it is only elicited when intense noxious stimuli threaten to injure tissue (Woolf 1995). It is characterized by a high stimulus threshold , is well localized and transient, and demonstrates a stimulus-response relantionship similar to those of the other somatosensations (Woolf and Chong 1993).

Figure 2.

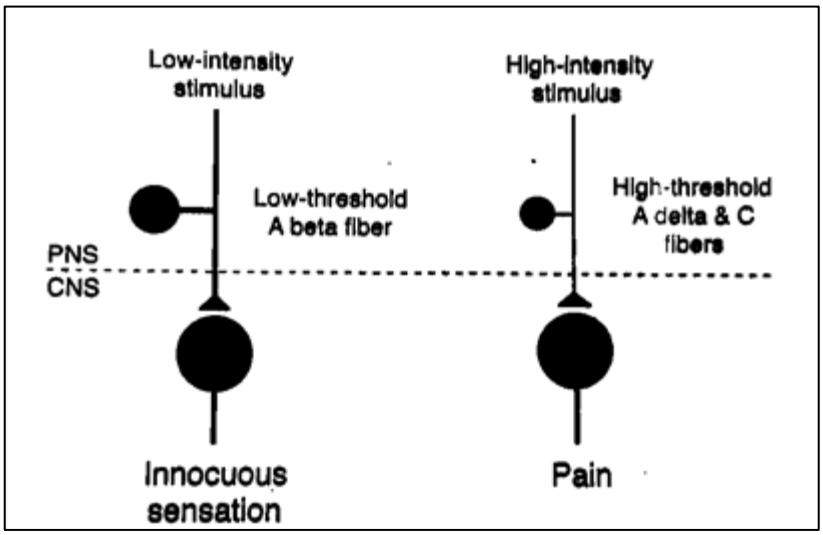


Fig. 2. *Functional specialization of primary sensory neurons enables, under normal circumstances, the responses to low- and high-intensity peripheral stimuli to be differentiated. The former activate low-threshold receptors generating innocuous sensations, and the latter activate high-threshold nociceptors, which can lead to the sensation of pain. This pain is a physiologic sensation, acting as a warning of potentially harmful stimuli. PNS = peripheral nervous system; CNS = central nervous system. From Woolf C and Chong M (1993).*

Nociceptive processing

The *nociception* is the physiologic component of pain and consists of the processes of transduction, transmission, and modulation of neural signals generated in response to an external noxious stimulus. It is a physiologic process resulting in the conscious perception of pain when completed. The simplest pathway is defined as a three-neuron chain, with the first-order neuron originating in the periphery and projecting to the spinal cord, the second-order neuron ascending the spinal cord, and the third-order neuron projecting to the cerebral cortex (Fig.3). On a more complex level, the pathway involves a network of branches and communications with other sensory neurons and descending inhibitory neurons from the midbrain that modulate afferent transmission of painful stimuli.

Figure 3.

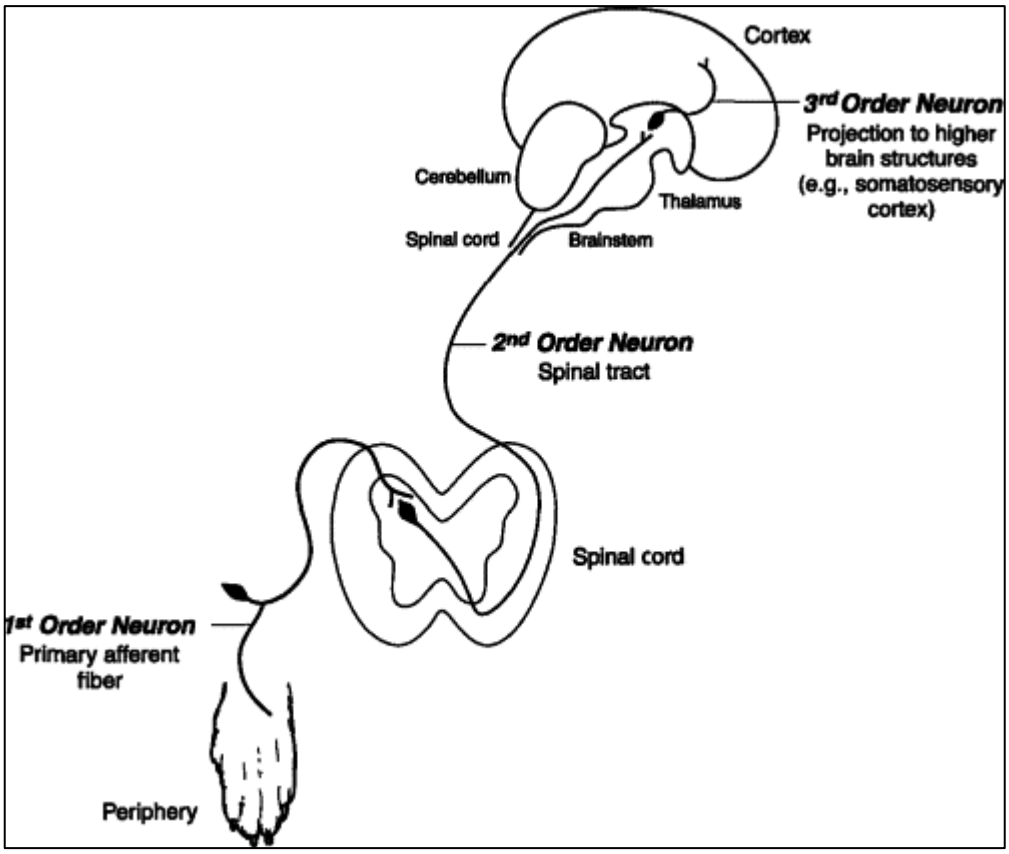


Fig. 3. *A simplified representation of nociceptive processing as a three-neuron chain. A noxious stimulus in the periphery activates a primary afferent fiber that transmits the information to the dorsal horn of the spinal cord. Here, a second order projection neuron that ascends in a spinal tract to the level of the thalamus intervenes. Finally, a tertiary neuron trasmits the modified noxious stimulus to higher brain centres, notably the cerebral cortex, for perception.*

Nociceptors are described as specialized nerve endings able to encode mechanical, chemical, or thermal energy into electric impulses in order to preserve tissue homeostasis by signalling actual or potential tissue injury (Sosnowski et al. 1992).There are two categories of nociceptors: A-fiber mechanoheat nociceptors and C-fiber mechanoheat (or polymodal) nociceptors. The first ones are responsible for signalling “first pain” which is well localized and transient, lasting only as long as the acute painful stimulus is activating the

nociceptor (Fielda 1987; Raja et al.1997). The second ones mediate “second” or “slow pain” which consists of a more diffuse and persistent burning sensation extending beyond the termination of an acute painful stimulus (Fig.4).

Figure 4.

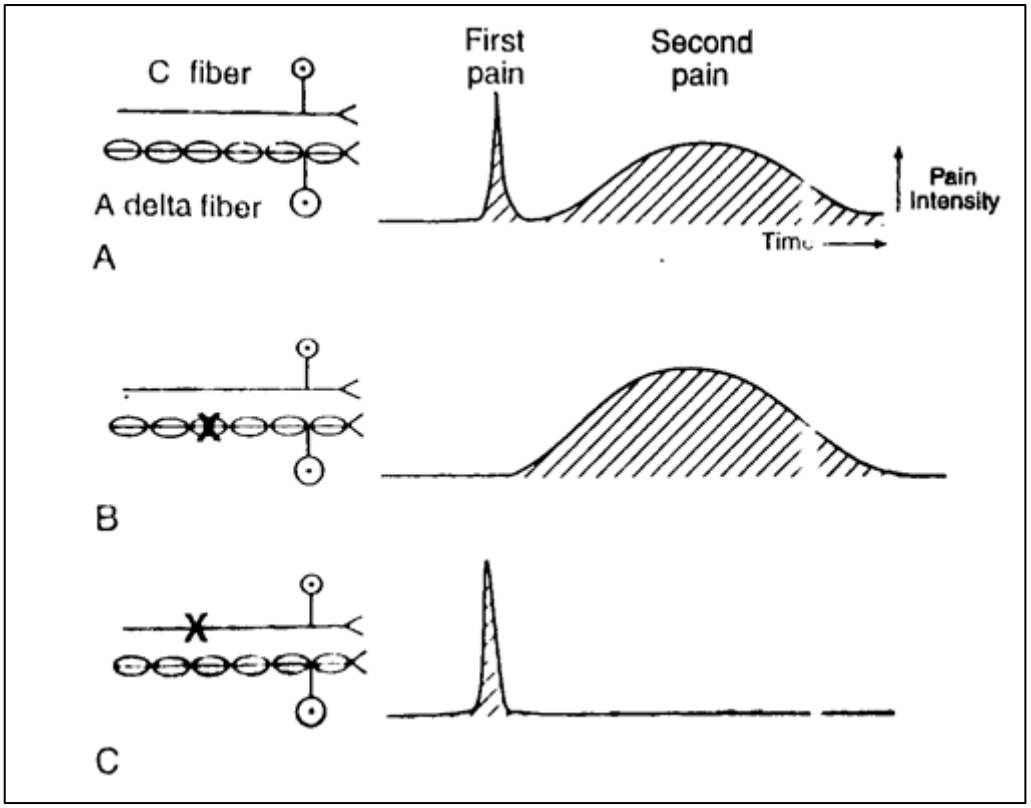


Fig. 4. *Primary afferent pain transmission. First pain and second pain sensations after a noxious stimulus (A). The first pain sensation is abolished when the A fibers are blocked (B), while the second pain sensation is abolished when the C fibers are blocked (C).*

Under certain circumstances, repeated activation of the nociceptors lowers their threshold and results in an enhanced response to subsequent stimuli (sensitization). Under other circumstances, repeated or sustained presentation of a noxious stimulus causes a diminished response (fatigue or habituation). Thus, a given stimulus induces a composite afferent message, resulting from the activation of various types of nociceptors with different thresholds and response characteristics.

The activation of nociceptors generates nociceptive signals which are transmitted to the central nervous system by their associated *afferent axons*. Aδ fibers are large diameter thinly

myelinated axons and conduct impulses rapidly (Jessell and Kelly 1991; Raja et al. 1997) facilitating the first pain signaled by the A fiber mechanoheat nociceptors. On the other hand, C fibers are smaller and unmyelinated and their transmission is slower and reinforce the quickly response of the Aδ fibers. The role of the C fibers becomes increasingly important as the duration of the stimulus persists.

Cell bodies of types of afferent nociceptive nerve fibers are contained in the dorsal root ganglia and extend axons to synapse with *dorsal horn neurons* within the gray matter of the spinal cord. The lamina I (or marginal zone) of the dorsal horn is the most superficial layer with the most of the Aδ fibers terminations (some fibers project more deeply to lamina V). The majority of C fibers terminates in the lamina II (or substantia gelatinosa) instead. (Fig.5).

Figure 5.

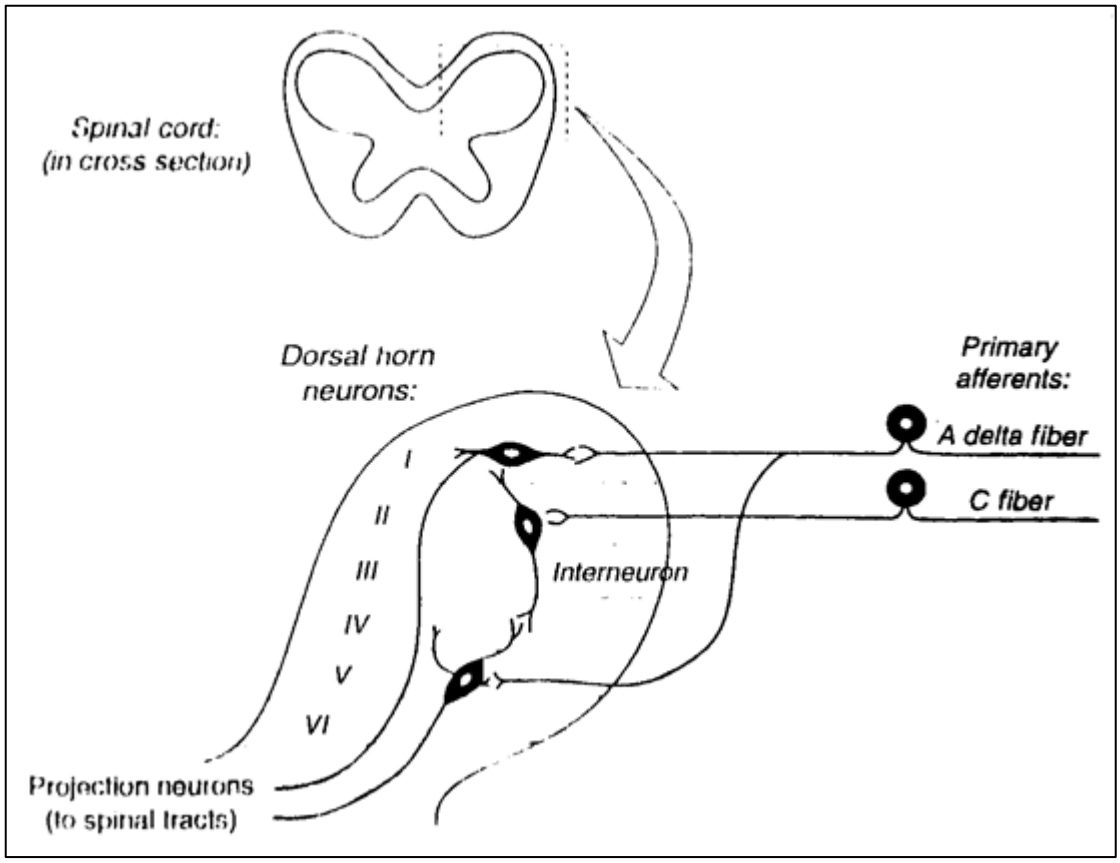


Fig. 5. *Laminar organization of spinal cord dorsal horn. Primary afferent fibers of nociceptors terminate on projection neurons in the dorsal horn of the spinal cord. Projection neurons in lamina I and lamina V receive direct input from myelinated Aδ fibers and indirect input from unmyelinated C fibers via interneurons in lamina II.*

Primary afferent axons may form direct or indirect connections with one of three functional populations of dorsal horn neurons: interneurons (excitatory and inhibitory), propriospinal neurons and projection neurons which participate in rostral transmission. There are three subtypes of projection neurons: nociceptive-specific (NS) neurons which are excited by noxious mechanical or thermal stimulus and are located in lamina I; wide dynamic range (WDR) neurons that receive innocuous input from low-threshold mechanoreceptors as well as nociceptive information and are concentrated in lamina V (Sorkin and Carlton 1997); complex neurons that are believed to be in lamina VII and integrate somatic and visceral activity (Cousins 1986; Cross 1994; Sorkin and Carlton 1997; Carroll 1999).

Within the dorsal horn, excitatory and inhibitory amino acids and neuropeptides mediate the communication of nociceptive information between many neurons. These neurotransmitters are produced, stored and released in the terminals of afferent nerve fibers and dorsal horn neurons (Jessell and Kelly 1991; Raffe 1997; Sorkin and Carlton 1997) .

Projection neurons transmit dorsal horn nociceptive input to supraspinal centers. The most important nociceptive pathway is called *spino-thalamic tract* (STT) (Fig. 6): the axons of NS and WDR neurons in laminae I, V, VI, and VII cross the midline and run in the anterolateral white matter, ultimately terminating in the thalamus. One group of STT axons projects into the lateral thalamic nuclei and transmits information from smaller and more discrete receptive fields in the periphery. These neurons are believed to play a role in the sensory discriminative aspects of pain. Axons projecting to the medial thalamic nuclei reflect input from larger and more diverse receptive fields and are implicated in the affective-motivational dimension of pain (Cross 1994; Thurmon et al. 1996).

Nociceptive neurons have been located in medulla, pons, midbrain, thalamus, hypothalamus and cerebral cortex.

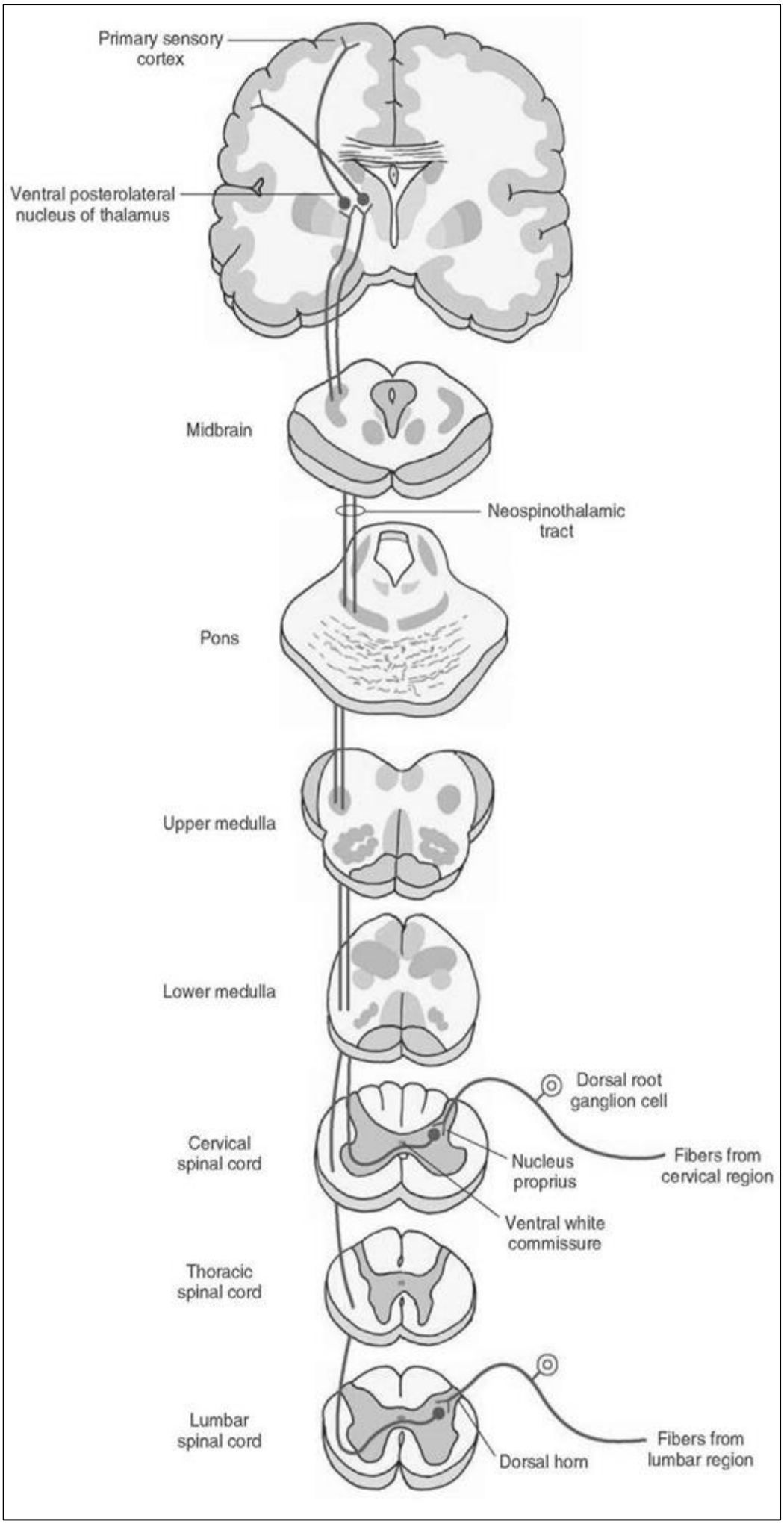
Figure 6.

Fig. 6. *The spinothalamic tract (also known as anterolateral system or the ventrolateral system) is a sensory pathway from the skin to the thalamus. From the ventral posterolateral nucleus in the thalamus, sensory information is relayed upward to the somatosensory cortex of the postcentral gyrus.*

The spinothalamic tract consists of two adjacent pathways: anterior and lateral. The anterior spinothalamic tract carries information about crude touch. The lateral spinothalamic tract conveys pain and temperature.

In the spinal cord, the spinothalamic tract has somatotopic organization. This is the segmental organization of its cervical, thoracic, lumbar, and sacral components, which is arranged from most medial to most lateral respectively.

The pathway decussates at the level of the spinal cord, rather than in the brainstem like the posterior column-medial lemniscus pathway and lateral corticospinal tract.


Primary sensory cortex
Ventral posterolateral nucleus of thalamus
Midbrain
Neospinothalamic tract
Pons
Upper medulla
Lower medulla
Dorsal root ganglion cell
Cervical spinal cord
Nucleus proprius
Fibers from cervical region
Ventral white commissure
Thoracic spinal cord
Lumbar spinal cord
Dorsal horn
Fibers from lumbar region

The nociceptive transmission is modulated by different and powerful inhibitory influences at many levels of the neuroaxis (Fig.7). This *descending modulatory system* is divided in four components: the cortical and thalamic structures, the periaqueductal gray matter (PAG) of the midbrain, the rostral medulla and pons of the brainstem, and the medullary and spinal cord dorsal horn (Jessell and Kelly 1991; Thirmon et al. 1996).

Figure 7.

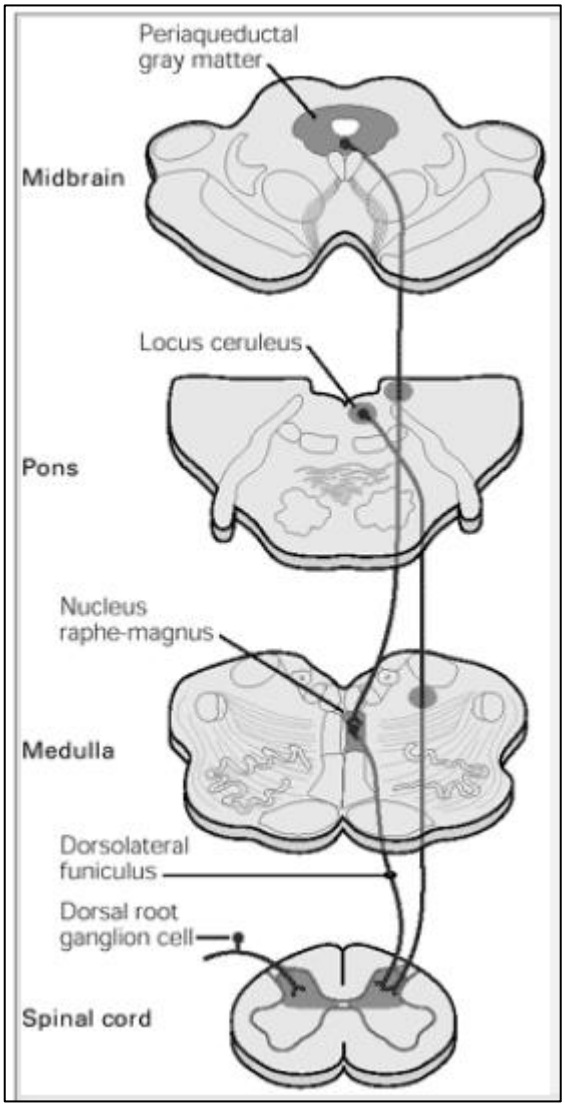


Fig. 7. *The descending modulatory system.*

Postoperative surgical pain is typically described as *acute pain*. Acute clinical pain is caused by soft tissue trauma and inflammation and has an important biological role as it facilitates tissue repair and healing. The reparative process can proceed because the injured area is hypersensitized (primary hyperalgesia) as well as the surrounding area (secondary hyperalgesia) (Woolf 1995).

Peripheral sensitization is an increased sensitivity to an afferent nerve stimulus. In that case, relatively benign noxious stimuli cause tissue inflammation that implies a releasing of sensitizing chemical mediators that have direct effect on the excitability of sensory and sympathetic fibers (Woolf 1989; Levine et al. 1993; Dray 1995; Siddall and Cousins 1995; Siddall and Cousins 1997; Willis and Coggeshall 1991 (Fig.8). All these molecules acting together are called “sensitizing soup” and lower the response threshold for Aδ and C fiber activation. These changes in the afferent transduction threshold are responsible for the zone of primary hyperalgesia surrounding the site of tissue damage.

Figure 8.

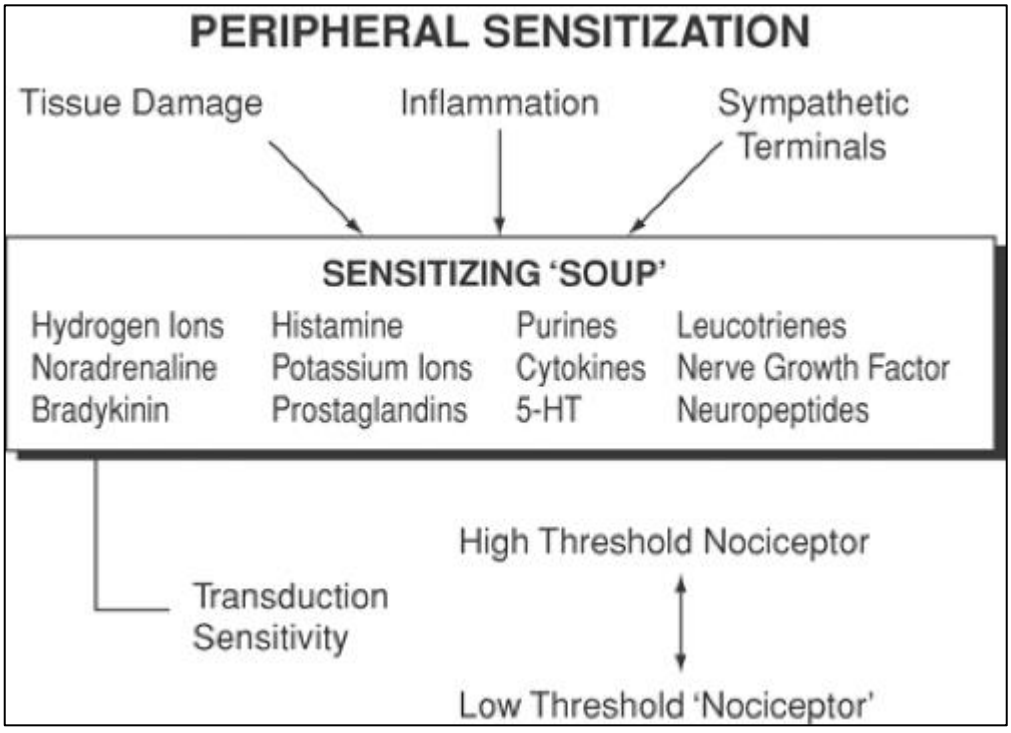


Fig. 8. *Transduction sensitivity of high-threshold nociceptors can be modified in the periphery by a combination of chemicals that act synergistically as a sensitizing soup. These chemicals are produced by damaged tissue as part of the inflammatory reaction and by sympathetic nerve terminals (Woolf and Chong 1993).*

According to IASP, *central sensitization* is "an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" (Loeser et al. 2008). Central sensitization describes the circumstances in which there is an enhancement of the function of neurons involved in nociception resulting in: hypersensitivity to stimuli, responsiveness to non-noxious stimuli (allodynia) and an increased pain response evoked by stimuli outside the area of injury, an expanded receptive field (zone of secondary hyperalgesia). Central sensitization is a result of dynamic changes in dorsal horn neuron excitability, which modifies their receptive field properties (Cousins 1986; Woolf and Chong 1993). Aδ and C fibers generate slow synaptic action potentials. The duration of these action potentials has an impact on dorsal horn neurons and this results in a summation of potentials during low-frequency repeated nociceptor inputs, creating a progressively increasing and long-lasting depolarization in dorsal horn neurons (*wind-up*) (Woolf and Chong 1993; Siddall and Cousins 1995; Woolf 1995). N-methyl-D-aspartate (NMDA) receptors mediate this wind-up as it is shown in figure 9.

Figure 9.

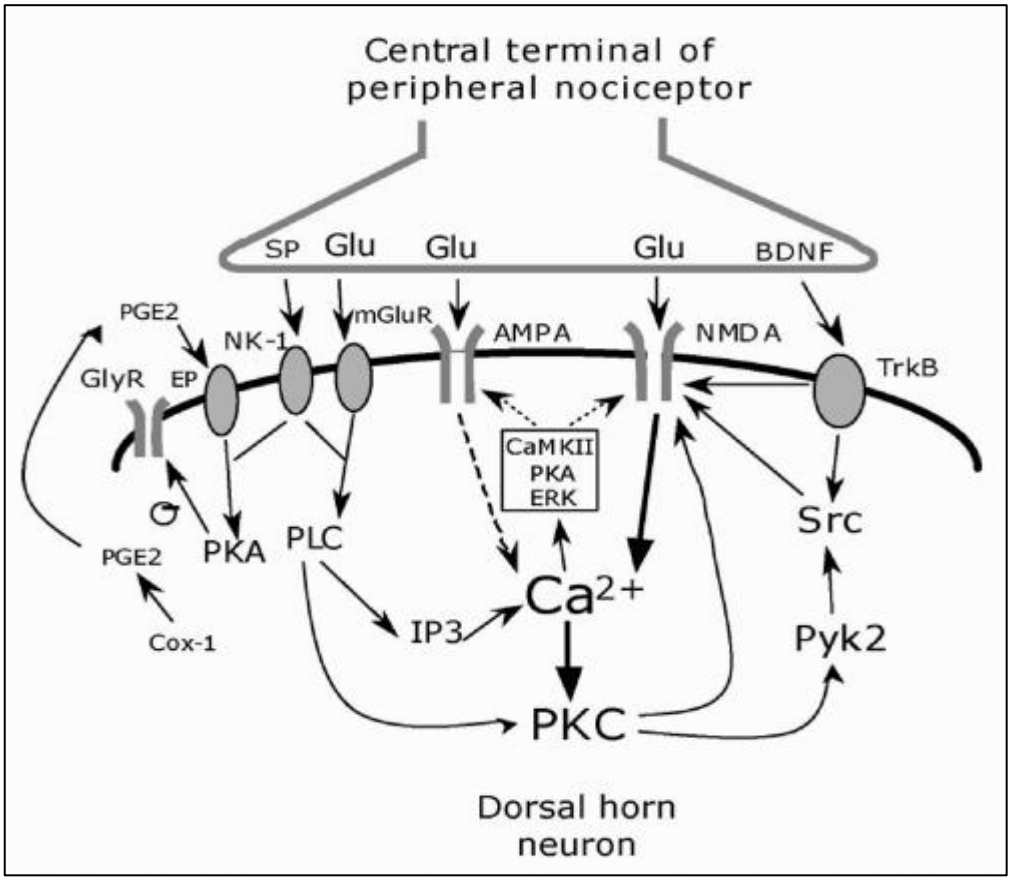


Fig.9. *The transmitter and cellular mechanisms that produce central sensitization. C fiber terminals release both the excitatory amino acid glutamate and neuropeptides such as the tachykininis in the dorsal horn of the spinal cord. Glutamate acts at N-methyl-D-aspartate (NMDA) receptors on postsynaptic membranes on dorsal horn neurons. Normally, the ion channel linked to the NMDA receptor is blocked by a magnesium ion, but the block can be removed by a depolarization of the cell leading to an influx of calcium and sodium ions, which leads to a further depolarization. The tachykinins bind to neurokinin receptors NK1 and NK2, leading (via G-protein activation) to depolarization and to changes in second messagers. The former will directly act on the NMDA ion channel, but the latter acts indirectly via protein kinase C (PKC) activation. Therefore, there are a number of postsynaptic mechanisms that lead to positive feedforward and feedback changes that increase excitability. Changes in second messangers can also modify immediate early gene expression, potentially producing very prolonged alterations in function (Woolf and Chong 1993).*

Systemic responses to pain and injury

The main target of nociceptive information is the nervous system, but the following pain response is more complex and involves segmental and suprasegmental reflex responses ("*stress response*"). This results not only in vasoconstriction and in increased sympathetic tone, systemic vascular resistance, cardiac output through increases in stroke volume and heart rate, myocardial work through increases in metabolic rate and oxygen consumption, but also in decreased gastrointestinal and urinary tone, and increased skeletal muscle tone (Wright and Woodson 1990; Thurmon et al. 1996). As far as the endocrine response is concerned, there are a decrease in insulin and testosterone secretion and an increase in corticotropin, cortisol, antidiuretic hormone, growth hormone, cyclic adenosine monophosphate, catecolamines, renin, angiotensin II, aldosterone, glucagon, and interleukin 1 secretion. The metabolic response includes a catabolic state with hyperglycemia, increased protein catabolism and lipolysis, renal retention of water and sodium with increased potassium excretion, and decreased glomerular filtration rate (Wright and Woodson 1990). Increased respiratory rate drive is caused by nociceptive stimulation of brainstem centres, whereas at the diencephalic and cortical levels intense anxiety and

fear worsen the reflex sympathetic responses and increase blood viscosity, prolong clotting time, fibrinolysis, and platelet aggregation (Wright and Woodson 1990; Thurmon et al. 1996).

The magnitude and the duration of this so-called stress response are correlated to the degree of tissue injury. Although the stress response is an evolutionary adaptation to optimize survival in the immediate post-damage period, its persistence may be deleterious and may increase the patient morbidity. Therefore, any pain management strategy have the attenuation of the stress response as a goal.

Implications for pain management

Most clinical pain syndromes are complex as they involve diverse types of pain. Thus, the success of therapeutic intervention is maximized when preemptive analgesia and multimodal analgesia are considered.

Preemptive analgesia consists in preventing the establishment of central sensitization by initiating treatment before acute insult (Woolf and Chong 1993) (Fig.10).

Figure 10.

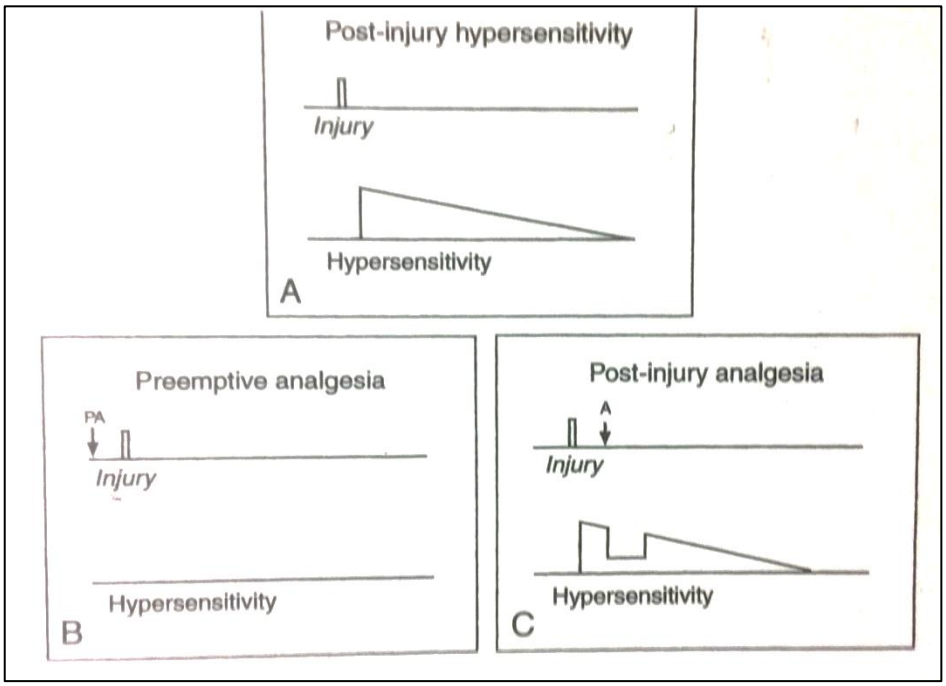


Fig. 10. *A simple model of the rationable behind single-treatment preemptive analgesia. Injury triggers central sensitization, leading to a prolonged hypersensitivity state (A). A preemptive analgesic (PA) prevents the ind*

uction of central sensitization, preempting the postinjury hypersensitivity (B). Postinjury analgesia (A) has a much diminished effect on an established state of hypersensitivity (C) (Woolf and Chong 1993).

Multimodal analgesia

Multimodal analgesia (or *balanced analgesia*) is defined as the strategy that combines different analgesic drugs and techniques in order to achieve not only beneficial additive or synergistic analgesic effects but also a reduction of side effects because lower doses are usually used (Kehlet and Dahl 1993; Brodner et al. 1998).

With this in mind, many diverse analgesic agents can be given to block or reduce the nociceptive processes of transduction, transmission, and modulation and thus the perception of pain (Fig.11).

Figure 11.

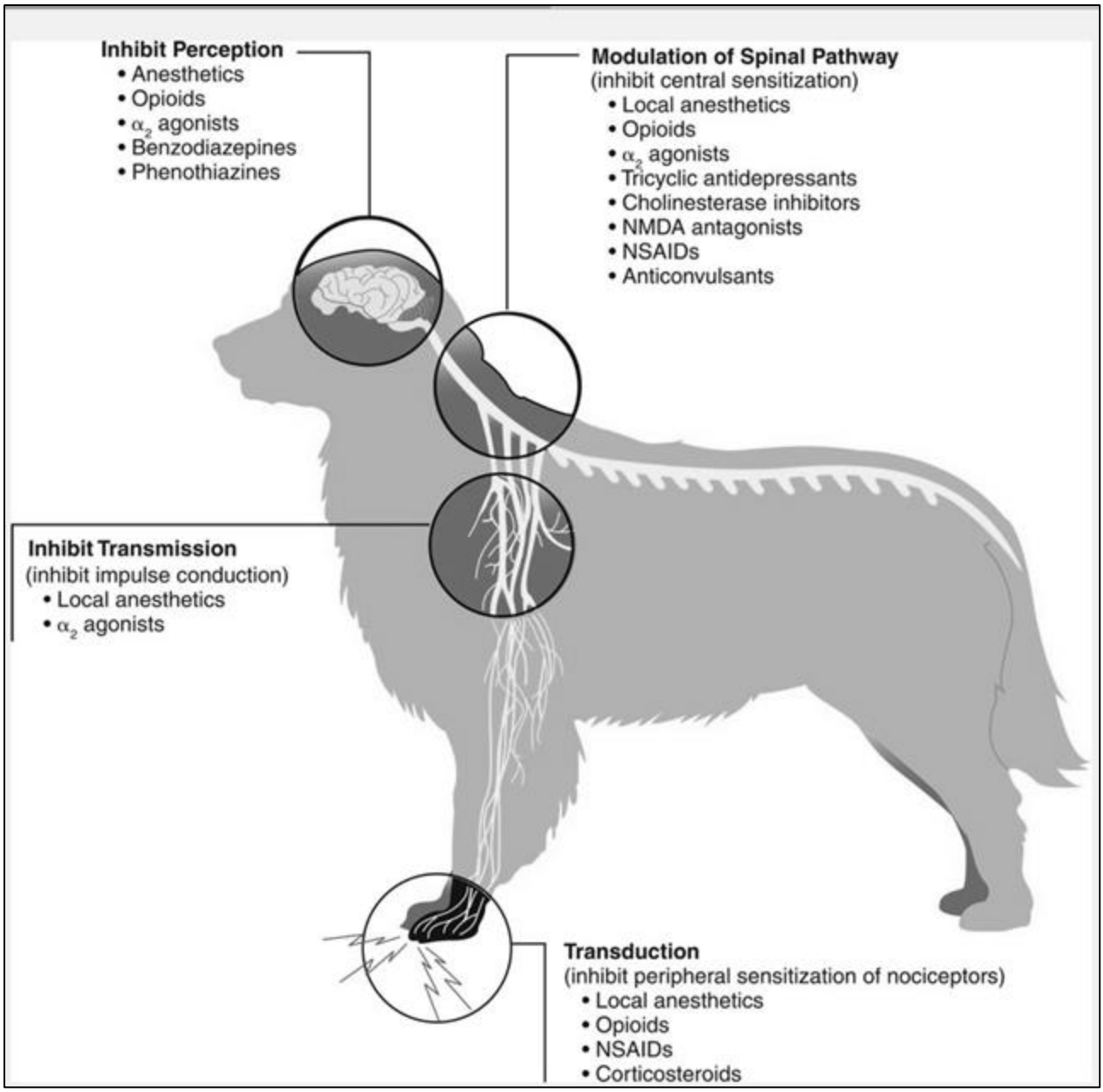

Inhibit Perception
• Anesthetics
• Opioids
• α_2 agonists
• Benzodiazepines
• Phenothiazines
Modulation of Spinal Pathway
(inhibit central sensitization)
• Local anesthetics
• Opioids
• α_2 agonists
• Tricyclic antidepressants
• Cholinesterase inhibitors
• NMDA antagonists
• NSAIDs
• Anticonvulsants
Inhibit Transmission
(inhibit impulse conduction)
• Local anesthetics
• α_2 agonists
Transduction
(inhibit peripheral sensitization of nociceptors)
• Local anesthetics
• Opioids
• NSAIDs
• Corticosteroids

Fig.11. *The sites of action of the major classes of analgesics as they affect transduction, transmission, and modulation of nociceptive input and the perception of pain. NSAIDs = nonsteroidal anti-inflammatory drugss; NMDA = N-methyl-D-aspartate.*

Phenothiazines

Acepromazine is a phenothiazine derivative antipsychotic drug. It has actions at all levels of the central nervous system, primarily at subcortical levels as well as on multiple organ systems. It has been shown to have strong antiadrenergic and weaker peripheral anticholinergic activity. Its mechanism of action consists in acting as antagonist on different postsynaptic receptors (dopaminergic, serotonergic, histaminergic, alpha1/alpha2, cholinergic).

Acepromazine is commonly administered via the subcutaneous or intramuscular route. It have high plasma protein bound and it is metabolised in the liver, while conjugated and unconjugated metabolites are excreted in urine. This phenothiazine causes a dose-dependent decrease in haematocrit, probably due to increased sequestration of red blood cells by the spleen. Decreased respiratory rate and lower arterial blood pressure may be noticed as well as a vagally-induced bradycardia and transient sinoatrial arrest (Plumb and al. 2002).

The recommended dose for dogs is 0.005-0.03 mg kg^{-1} IM, IV or SC. Acepromazine is widely used as a pre-anaesthetic sedative in dogs, decreases dose of general anaesthesia, and makes induction and recovery smooth. It is not suitable for use as a premedication prior procedures which may promote epileptiform seizures (myelography) as well as premedication of animals known to be epileptic. Its use in trauma patients is unsuitable because it may cause hypotension which can be fatal in hypovolaemic dogs. Besides, it is contraindicated in pregnant female animals and it must be used with caution, and decreased dosage, in individuals with general debilitation, hepatic dysfunction or cardiac disease, and in the very young. Adverse effects are namely hypotension, thrombocytopaenia, platelet dysfunction, ataxia and muscle tremors, hypothermia. In brachycephalic breeds of dogs it may cause syncope.

Opioids

Opioids have provided the most effective analgesia for many years and are still the best drugs available for pain management in cats and dogs.

There are at least three different kind of opioid receptors with different roles in the nervous system (Fig.12). Although the receptors are generally classified as mu, kappa, and delta, it is becoming obvious that there are several subtypes of each of these receptors and that the expression of these receptors varies according to the location of the tissue. The drugs we use have different affinities for these receptors, and this explains some of the differences between the opioids (Fig.13).

Figure 12.

Fig.12. *Functional effects of mu, delta, and kappa opioid receptors.*

Analgesia	Mu	Delta	Kappa
Supraspinal	+++	-	-
Spinal	++	++	++
Peripheral	++	-	++
Resp. depression	+++	++	-
Miosis	++	-	+
GI motility	++	++	+
Euphoria	+++	-	-
Dysphoria	-	-	+++
Sedation	++	-	++
Dependence	+++	-	+

Drugs as morphine, methadone, fentanyl, hydromorphone, and meperidine are opioid agonists and act mainly at the mu receptors, where they have a high affinity. The agonist-antagonists (butorphanol, buprenorphine, and pentazocine) are able to reverse some of the effects of the pure agonists but are still capable of producing analgesia themselves. The receptor activity of these drugs is varied; for example, butorphanol seems to act at the kappa receptors and as mu antagonist, whereas buprenorphine is a kappa antagonist but has high affinity for mu receptors, although it only has moderate receptor activity and is classified as a partial agonist. It should be recognized that these drugs do tend to antagonize the pure agonists, and care maust be taken not to mix these two classes of opioids unless reversal of the agonist is intended. The antagonists include naloxone, naltrexone, and nalmefene. These drugs reverse the actions of both mu and kappa agonists, although their activity is more potent at the mu receptor.

The opioids can be used by sistemic administration or can be applied more directly to the tissues or the spinal receptors by injecting the drug epidurally or intrathecally.

Figure 13.

Fig. 13. *The receptor affinities of opioids at mu, kappa, and delta receptors.*

+ = low affinity; ++ = moderate affinity; +++ = high affinity.

	RECEPTOR TYPE		
Opioid	MOP	KOP	DOP
Clinical drugs			
Agonists			
✓Morphine	+++	+	+
✓Pethidine	+++	+	+
✓Diamorphine	+++	+	+
✓Fentanyl	+++	+	-
Partial agonists			
✓Buprenorphine	++	+	-
✓Pentazocine	-	++	-
Antagonists			
✓Naloxone	+++	++	++

Buprenorphine

Buprenorphine hydrochloride is a partial μ-opioid agonist and a synthetic derivative of thebaine. Structurally, it is similar to morphine. Because of its lipophilic nature, buprenorphine binds to the μ-opioid receptor slowly but with a high affinity; therefore, buprenorphine has a slow onset and long duration of action. Despite its high affinity for the μ-receptor, buprenorphine has only partial activity; therefore, it provides moderate analgesia and variable sedation and is associated with few adverse effects.

In veterinary medicine, buprenorphine is used primarily as an analgesic for relieving mild-to-moderate pain in dogs and cats following routine surgical procedures.

Studies investigating the analgesic effects of buprenorphine have shown that the addition of an NSAID greatly enhances overall pain control (Shin et al. 2008; Steagall et al. 2014); hence, the current recommendation is to combine buprenorphine with an NSAID for surgical pain management in healthy patients.

In dogs, buprenorphine is metabolized predominantly in the liver, with the major route of elimination being biliary excretion into the feces.

Compared with full μ-opioid agonists, buprenorphine has some distinct disadvantages. One major drawback is the drug's high affinity for the μ-opioid receptor, which inhibits the effects of full μ-opioid agonists used concurrently. Another disadvantage is the slow onset of action.

Recommended dosing for both species is 0.01 to 0.04 mg kg^{-1} (higher doses for sustained-release and high-concentration formulations) q6-12h IV, IM, or SC. However, pain management protocols involving buprenorphine should tailor dose regimens to patient status and pain level rather than using predetermined dosing intervals.

Buprenorphine has many unique characteristics that distinguish it from other μ-opioid agonists with significant clinical advantages. It has a long duration of action with good to moderate analgesia and few side effects in dogs and cats. Buprenorphine can cause clinically insignificant cardiovascular changes, such as mild bradycardia and hypotension. It has minimal respiratory depressant effects and is not associated with clinically significant hyperthermia in cats. Larger doses of buprenorphine are not associated with an increased level of sedation or adverse effects (eg, potential bradycardia, mild respiratory depression).

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a drug class that groups together drugs that provide analgesic and antipyretic effects, and, in higher doses, anti-inflammatory effects.

The most prominent members of this group of drugs are aspirin, ibuprofen and naproxen. Most NSAIDs inhibit the activity of ciclooxygenase and tromboxanes (Fig.14). It is thought that inhibiting COX-2 leads to the anti-inflammatory, analgesic and antipyretic effects and that those NSAIDs also inhibiting COX-1, particularly aspirin, may cause gastrointestinal bleeding and ulcers (Clive et al. 1998) (Fig.15).

NSAIDs are usually used for the treatment of acute or chronic conditions where pain and inflammation are present.

Aspirin, the only NSAID able to irreversibly inhibit COX-1, is also indicated for inhibition of platelet aggregation. This is useful for the management of arterial thrombosis and prevention of adverse cardiovascular events. Aspirin inhibits platelet aggregation by inhibiting the action of thromboxane A2.

Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. This inhibition is competitively reversible, as opposed to the mechanism of aspirin, which is irreversible inhibition (Knights 2013). COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A2). Prostaglandins act (among other things) as messenger molecules in the process of inflammation. This mechanism of action was elucidated by John Vane (1927–2004), who received a Nobel Prize for his work.

COX-1 is a constitutively expressed enzyme with a "house-keeping" role in regulating many normal physiological processes. One of these is in the stomach lining, where prostaglandins serve a protective role, preventing the stomach mucosa from being eroded by its own acid. COX-2 is an enzyme facultatively expressed in inflammation, and it is inhibition of COX-2 that produces the desirable effects of NSAIDs.

When nonselective COX-1/COX-2 inhibitors (such as aspirin, ibuprofen, and naproxen) lower stomach prostaglandin levels, ulcers of the stomach or duodenum internal bleeding can result.

NSAIDs have been studied in various assays to understand how they affect each of these enzymes. While the assays reveal differences, unfortunately, different assays provide differing ratios.

The discovery of COX-2 led to research to the development of selective COX-2 inhibiting drugs that do not cause gastric problems characteristic of older NSAIDs.

However, many aspects of the mechanism of action of NSAIDs remain unexplained, and for this reason, further COX pathways are hypothesized. The COX-3 pathway was believed to fill some of this gap but recent findings make it appear unlikely that it plays any significant role in humans and alternative explanation models are proposed (Hinz et al. 2008).

NSAIDs interact with the endocannabinoid system and its endocannabinoids, as COX2 have been shown to utilize endocannabinoids as substrates, and may have a key role in both the therapeutic and adverse effects of NSAIDs, as well as in NSAIDs-induced placebo responses (Rouzer et al. 2008; Hamza et al. 2009; Fowler 2017).

Figure 14.

Fig.14. *Arachidonic acid metabolism.*

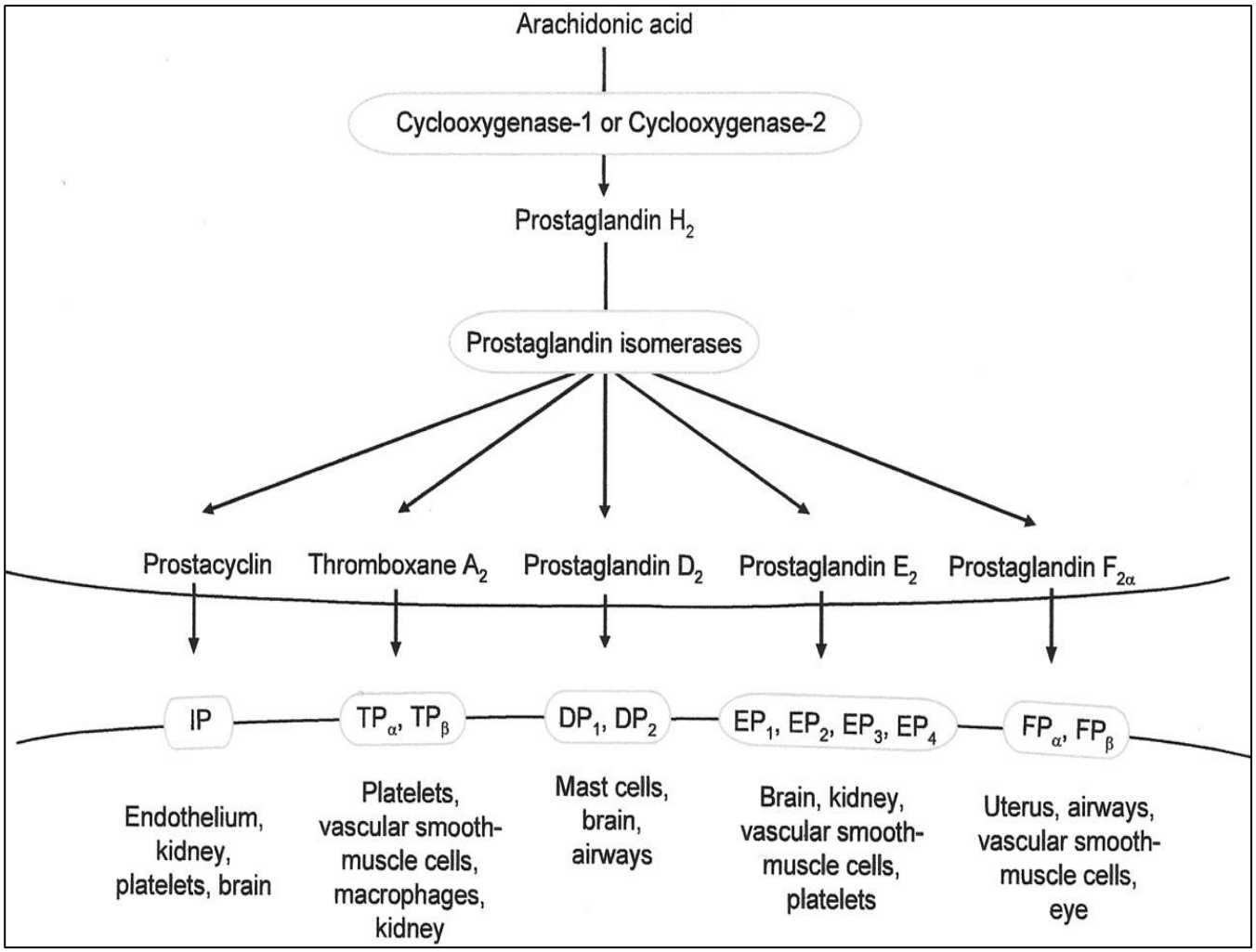
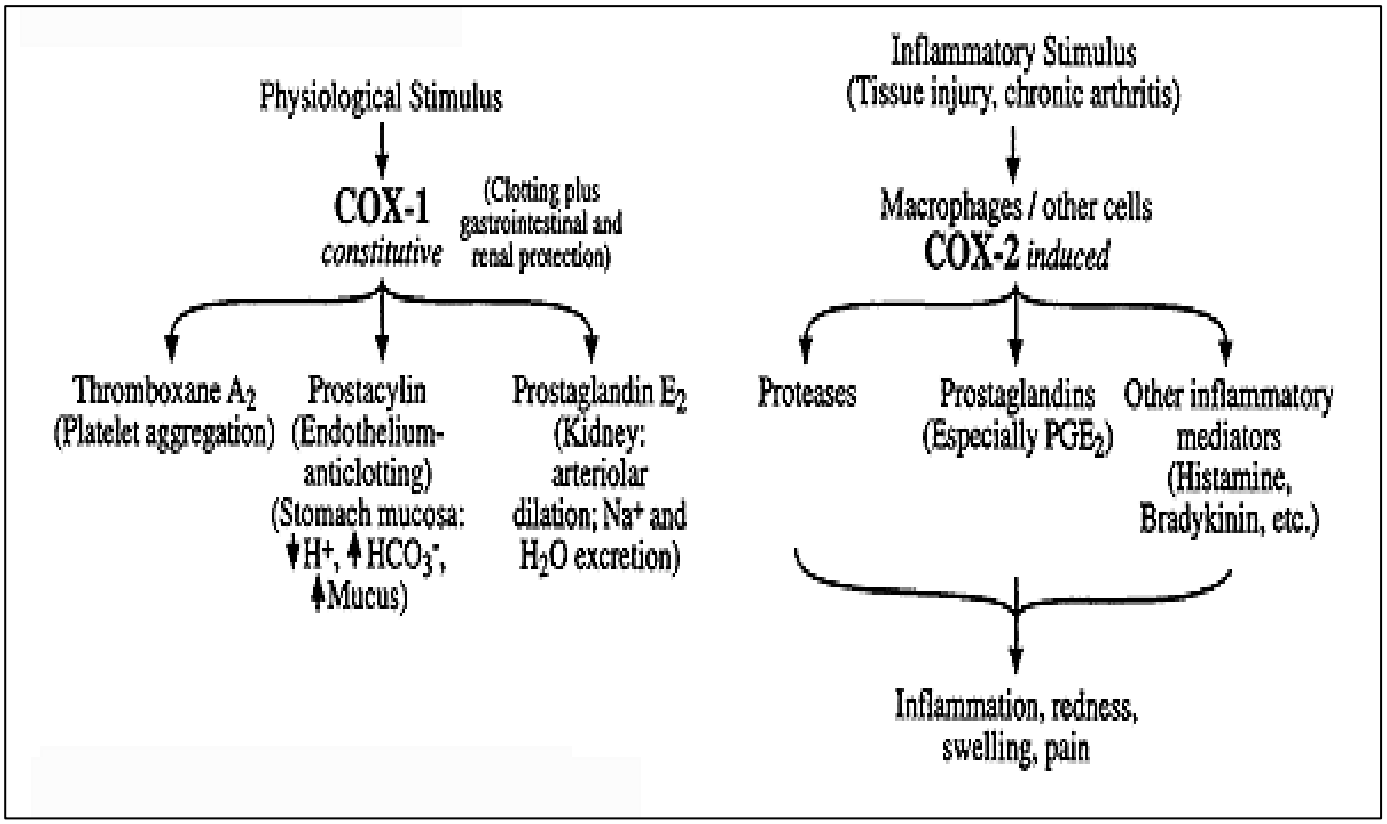


Figure 15.

Fig.15. *Arachidonic acid metabolism.*



Carprofen

Carprofen is a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen. The mechanism of action of Carprofen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals. The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-l is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity. In an in vitro study using canine cell cultures, Carprofen demonstrated selective inhibition of COX-2 versus COX-1 (Ricketts A et al. 1998). Clinical relevance of these data has not been shown.

Carprofen is eliminated in the dog primarily by biotransformation in the liver followed by rapid excretion of the resulting metabolites in the feces (70-80%) and urine (10-20%).

Carprofen is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclooxygenase which is responsible for the formation of prostaglandins from arachidonic acid. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients. The most frequently adverse effects have been gastrointestinal signs. Events involving suspected renal, hematologic, neurologic, dermatologic, and hepatic effects have also been reported. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction.

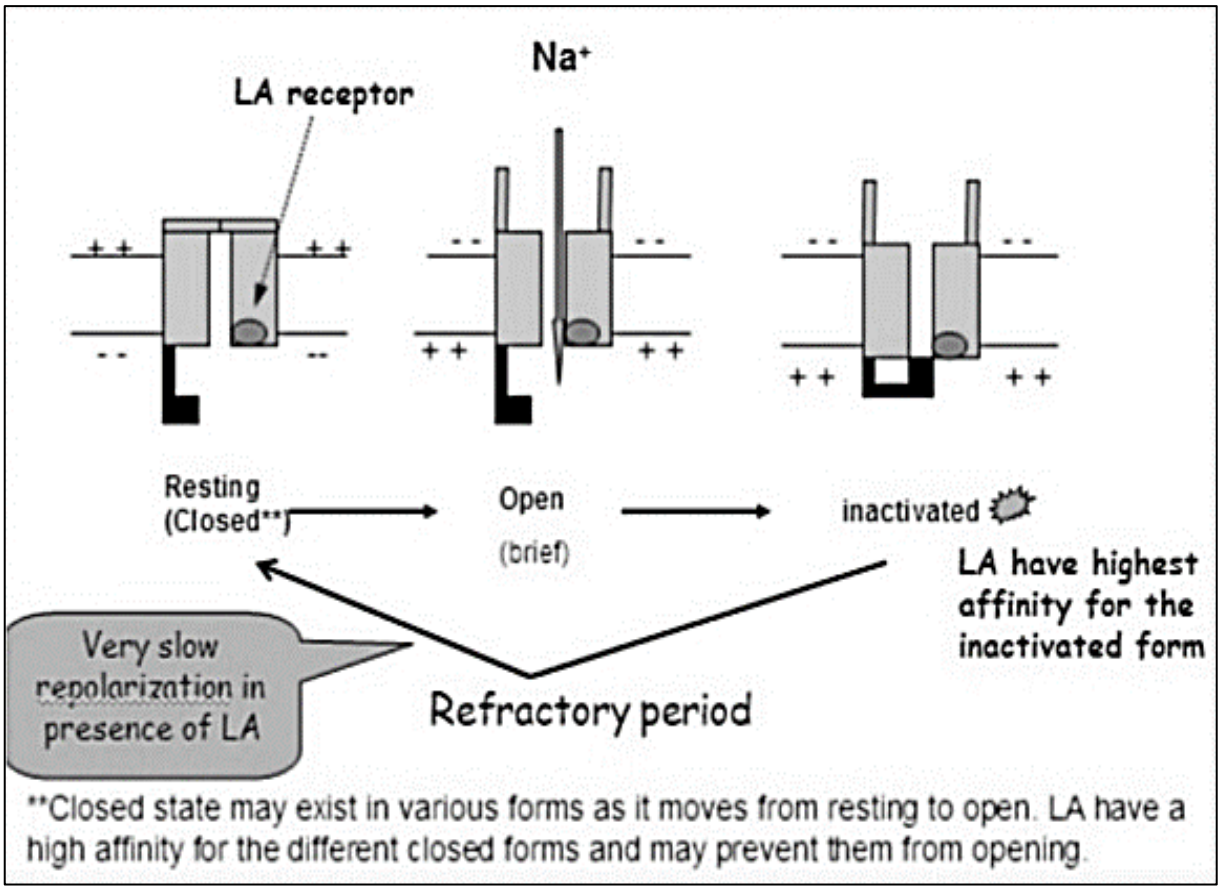
The total daily dose may be administered IV or SC as 4 mg kg^{-1} of body weight once daily or divided and administered as 2 mg kg^{-1} twice daily.

Local anaesthetics and other adjuncts

Local anesthetics produce anesthesia by inhibiting excitation of nerve endings or by blocking conduction in peripheral nerves. This is achieved by anesthetics reversibly binding to and inactivating sodium channels. Sodium influx through these channels is necessary for the depolarization of nerve cell membranes and subsequent propagation of impulses along the course of the nerve. Thus, the open state of the sodium channel is the primary target of local anesthetic molecules. The blocking of propagated action potentials is therefore a function of the frequency of depolarization (Fig.16). The mechanism for differential block, the block of pain perception without motor block, is still unclear (Marhofer et al. 2011).

Figure 16.

Fig.16. *Mechanism of action of local anaesthetics.*



All local anesthetics have an intermediate chain linking an amine on one end to an aromatic ring on the other. The amine end is hydrophilic, and the aromatic end is lipophilic. Variation of the amine or aromatic ends changes the chemical activity of the drug.

Two basic classes of local anesthetics exist, the amino amides and the amino esters. Amino amides have an amide link between the intermediate chain and the aromatic end, whereas amino esters have an ester link between the intermediate chain and the aromatic end.

Amino esters and amino amides differ in several respects. Amino esters are metabolized in the plasma via pseudocholinesterases, whereas amino amides are metabolized in the liver. Amino esters are unstable in solution, but amino amides are very stable in solution. Amino esters are much more likely than amino amides to cause allergic hypersensitivity reactions.

Commonly used amino amides include lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, and ropivacaine and levobupivacaine (Lam et al. 2011; Grider et al. 2011).

Commonly used amino esters include cocaine, procaine, tetracaine, chloroprocaine, and benzocaine. The newest additions to clinically available local anesthetics, namely ropivacaine and levobupivacaine, represent exploitation of the S enantiomer of these chemicals to create anesthetics which are less toxic, more potent, and longer acting.

Physiologic activity of local anesthetics is a function of their lipid solubility, diffusibility, affinity for protein binding, percent ionization at physiologic pH, and vasodilating properties.

Lipid solubility is an important characteristic. Potency is directly related to lipid solubility, because 90% of the nerve cell membrane is composed of lipid. Increased lipid solubility leads to faster nerve penetration and blockade of sodium channels.

Diffusibility of the local anesthetic through tissue other than nerve tissue also influences the speed of action onset.

Protein binding is related to the duration of action. The more firmly the local anesthetic binds to the protein of the sodium channel, the longer the duration of action.

Local anesthetics exist in ionized and non-ionized forms, the proportions of which vary with the pH of the environment. The non-ionized portion is the form that is capable of diffusing across nerve membranes and blocking sodium channels. Anesthetics with presence of greater non-ionized portions have a faster onset of action. Local anesthetics differ in respect to the pH at which the ionized and non-ionized forms are present at equilibrium, but this pH is generally in the range of 7.6-8.9. The more closely the equilibrium pH for a given anesthetic approximates the physiologic pH of tissues (ie, 7.35-7.45), the more rapid the onset of action. A decrease in pH shifts equilibrium toward the ionized form, delaying onset of action. This explains why local anesthetics are slower in onset of action and less effective in the presence of inflammation, which creates a more acidic environment with lower pH. Contrastingly, the addition of sodium bicarbonate is used clinically to increase the pH of local anesthetic solutions thereby enhancing onset of action. Overzealous alkalinization, however, can cause local anesthetic molecules to precipitate from solution.

All local anesthetics, with the exception of cocaine, are vasodilators. Vasodilation occurs via direct relaxation of peripheral arteriolar smooth muscle fibers. Greater vasodilator activity of a local anesthetic leads to faster absorption and, thus, shorter duration of action.

For proper administration of local anesthetics, consider the individual characteristics of the patient, dose of local anesthetic to be administered, presence or absence of epinephrine, speed of administration, local tissue vascularity, and technique of administration.

Adverse reactions may occur following administration of local anesthetics and usually result from administration of too much drug. Adverse reactions may also occur following injection of very vascular sites or from accidental direct intravascular injection of the drug. Deaths following local anesthetic administration are always a result of overdosage.

Tissue toxicity can be achieved by all local anesthetics if "high" concentrations are used. Adverse reactions occur primarily in the CNS (neurotoxicity) and cardiovascular system (myotoxicity) because these tissues are also composed of excitable membranes, the target of local anesthetic action. Local anesthetics decrease the rate of depolarization of cardiac tissue, which is the rationale behind the use of lidocaine in treatment of ventricular arrhythmias. At higher concentrations, amplitude of the cardiac action potential is decreased, and the velocity of conduction is reduced. At toxic doses, the negative inotropic effects of local anesthetics may lead to bradycardia, ventricular fibrillation, or asystole. Other cardiovascular effects include hypotension, which occurs via the direct vasodilating effects of local anesthetics on peripheral arteriolar smooth muscle. In the CNS, a progression of signs and symptoms may be observed in the animal. Upon examination, the patient may develop nystagmus. At higher levels of anesthetics, the patient may become anxious and develop fine tremors of the muscles. These tremors may worsen and coalesce into a grand mal seizure. Ultimately, the patient may experience generalized CNS depression leading to hypoxia, acidosis, and respiratory arrest.

Ropivacaine HCl

Ropivacaine HCl as a member in the amino amide class of local anesthetics, blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination and conduction velocity of affected nerve fibers.

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation and is mainly excreted by the kidney.

Unlike most other local anesthetics, the presence of epinephrine has no major effect on either the time of onset or the duration of action of ropivacaine. Likewise, addition of epinephrine to ropivacaine has no effect on limiting systemic absorption of ropivacaine.

Systemic absorption of rpivacaine can produce effects on the central nervous and cardiovascular systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance have been reported. Toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias and to cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression or both. Apparent central stimulation is usually manifested as restlessness, tremors and shivering, progressing to convulsions, followed by depression and coma, progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited stage.

Ropivacaine has a long-lasting action. At low concentrations (0.25-0.5%) ropivacaine is similar to bupivacaine for slow onset, but at higher concentrations (0.75%) the onset is as fast as that of mepivacaine. Ropivacaine (0.5%) provides sensory blockade as bupivacaine, but it is less likely to produce motor block (Hadzic and Vloka 2004). All these proprieties make ropivacaine a very useful drug for neuroaxial anaesthesia.

The smallest dose and concentration required to produce the desired result should be administered. As for any local anaesthetics, the dose of ropivacaine varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of

muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. Duke and collegues (2000) found that the epidural administration of 0.5% ropivacaine (0.22 mg kg^{-1}) provided sensory blockade for 115 minutes in dogs.

Ropivacaine is indicated for the production of local or regional anesthesia (epidural injection, major nerve blocks, and local infiltration) for surgery and for acute pain management (epidural continuous or intermittent bolus and local infiltration).

In performing ropivacaine blocks, unintended intravenous injection is possible and may result in cardiac arrhythmia or cardiac arrest.

Magnesium

Within the last twenty years, there has been an increasing interest to multimodal approach to pain in veterinary patients, especially with respect to the use of agents which, despite not being listed among classical analgesic agents, exert antinociceptive effects (Kukanich 2013; Madden et al. 2014; Crociolli et al. 2015; Norkus et al. 2015). Among these, magnesium plays a central role in the prevention of central sensitization by blocking the dorsal horn NMDA (N-methyl-D-aspartate) receptors in a non-competitive, voltage dependent fashion (Fig.17). Magnesium sulphate is inexpensive, and available in Europe as a formulation that is stable at room temperature and which use is approved for parenteral administration in dogs. The potential for neurotoxicity when magnesium is administered intrathecally was investigated in dogs, and neurological impairment and histopathological lesions of the spinal cord were not found after a dose of 3 mg kg^{-1} (Simpson et al. 1994). The studies investigating the clinical role of magnesium as adjuvant in pain therapy show conflicting results. Intravenous magnesium failed to improve perioperative pain in both humans and dogs (Murphy et al. 2013; Rioja et al. 2012). Conversely, several clinical trials showed that magnesium effectively improves analgesia in human patients receiving combinations of local anaesthetics and opioids, by either epidural or spinal route (Buvanendran et al. 2002; Oezalevli et al. 2005; Arcioni et al. 2007). The antinociceptive effects of epidural magnesium were demonstrated experimentally in dogs (Bahrenberg et al. 2015), however there is a paucity of data regarding the clinical use of magnesium in this species. A clinical trial suggests that adding spinal magnesium to ropivacaine increases the duration and the intensity of analgesia, but also of the motor block, provided by ropivacaine alone in dogs undergoing orthopaedic surgery (Adami et al. 2016).

Figure 17.

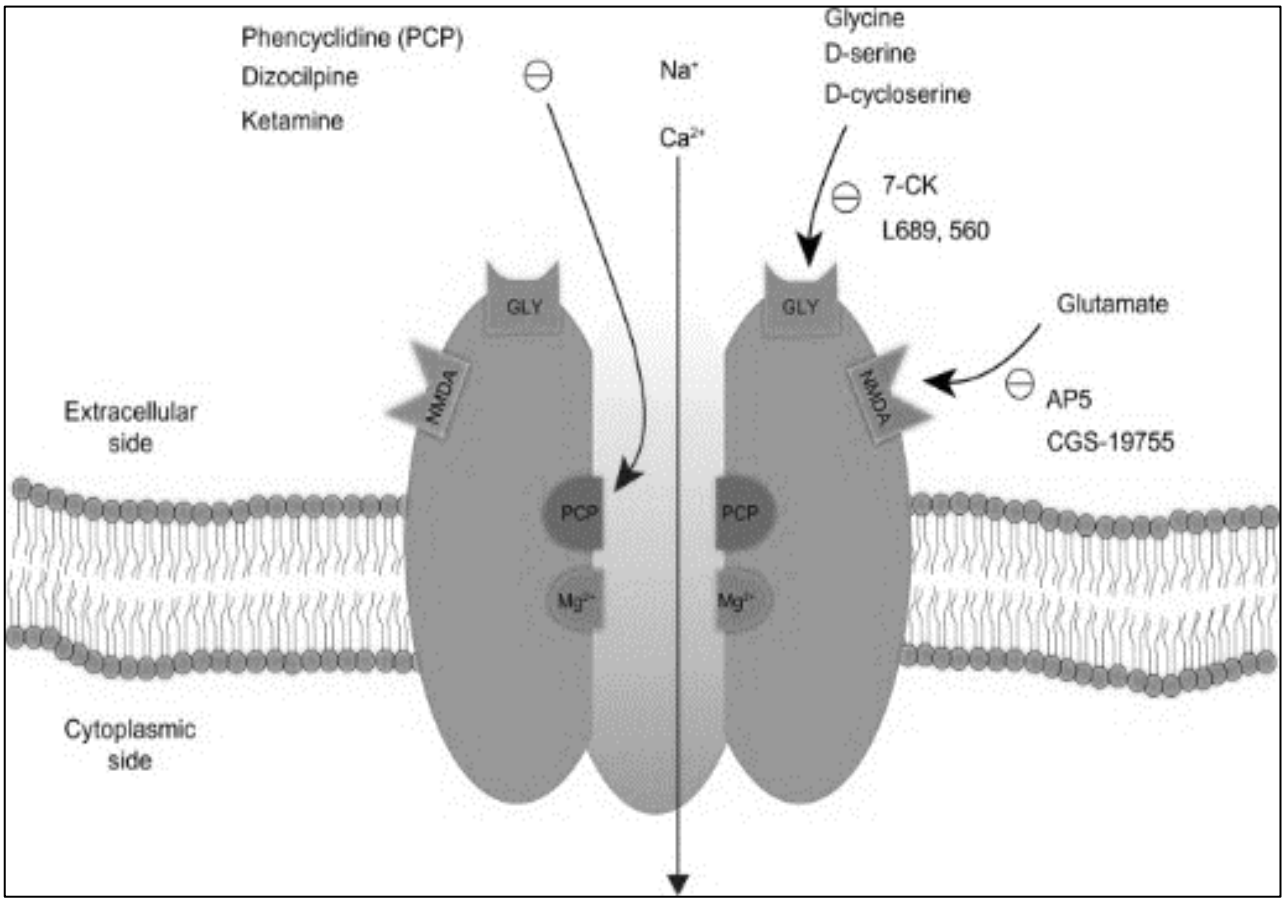


Fig.17. *Schematic diagram of NMDA receptor complex. The NMDA receptor is an ionotropic glutamate receptor for controlling synaptic plasticity and memory function.47,49 Glutamate (and NMDA) binds to the agonist site on the NMDA receptors. PCP, ketamine, and dizocilpine bind to the PCP receptor in the inside of the NMDA receptors. Glycine and D-serine bind to a glycine modulatory site on the NMDA receptors. The NMDA receptor is blocked by Mg2+ in a voltage sensitive manner. Activation of NMDA receptor by binding of both glutamate and glycine results in the opening of the channel. This allows voltage-dependent flow of Na+ and small amounts of Ca2+ ions into the cell and K+ out of the cell. The symbol (−) denotes inhibitory effect. Abbreviations: NMDA, N-methyl-D-aspartate; 7-CK, 7-chlorokynurenic acid; L689,560, trans-2-carboxy-5,7-dichloro-4-phenylaminocarbonyl; AP5, 2-amino-5-phosphonovaleric acid; CGS-19775, cis-4-phosphonomethyl-2-piperidinecarboxylic acid.*

Loco-regional anaesthesia

Recently, loco-regional anaesthesia has become popular in veterinary medicine to provide intra- and postoperative pain control. With a growing interest on improving pain management for pets, many loco-regional techniques that were originally used in human beings now are adapted to animals with success (Campoy et al. 2008; Figueiredo et al. 2008; Bardell et al. 2010; Mosing et al. 2010; Zarucco et al. 2010; Watts et al. 2011).

Loco-regional anaesthetic techniques are divided in *peripheral* (i.e. regional and plexus blocks, intravenous regional anaesthesia (IVRA), infiltration anaesthesia) and *neuraxial,* namely spinal and epidural injections.

As an alternative to systemic analgesia, loco-regional anaesthetic techniques offer the advantage of a selective and targeted block of the anatomical area of interest, resulting in better pain management and sooner discharge.

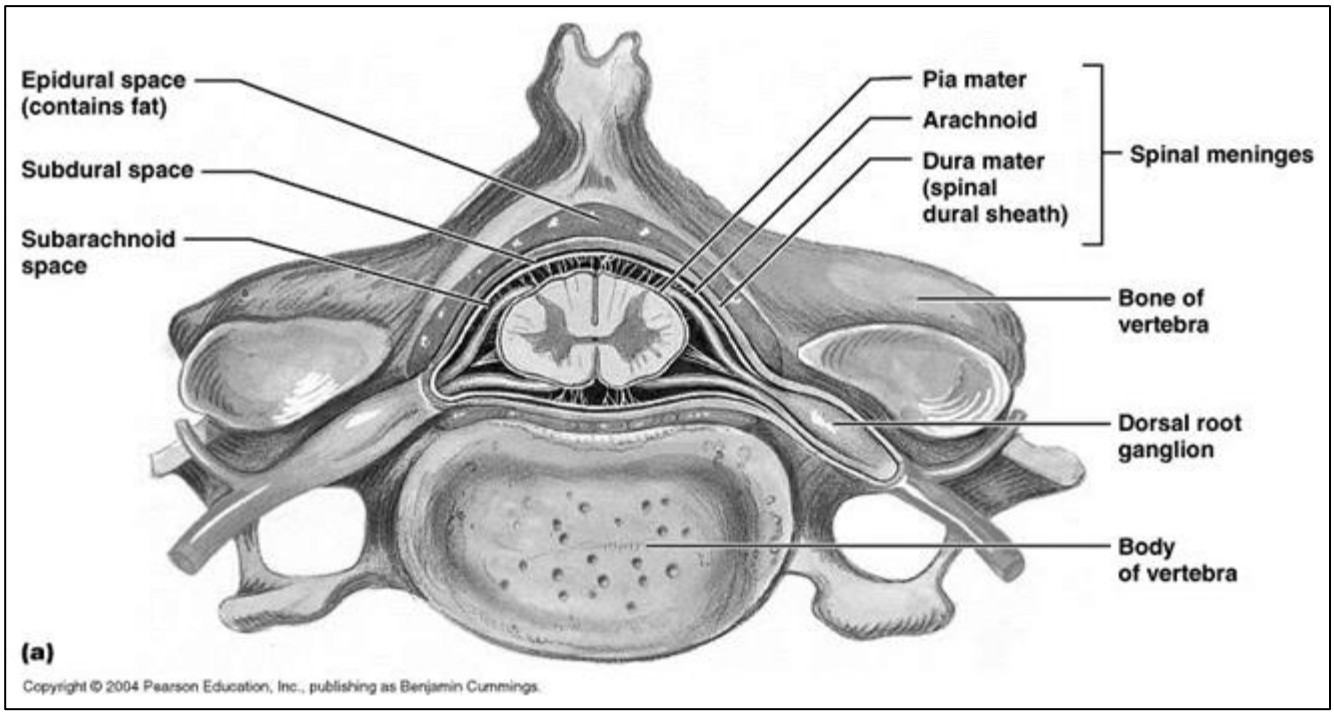
Loco-regional techniques are safe with a well-trained operator and proper equipment. Complications are rare and are broadly categorized as being either systemic toxicities (central nervous system symptoms and cardiovascular changes) or nerve injuries (neurological injuries, mechanical trauma and neuronal ischemia).

Epidural injection

"*Epidural*" (or extradural) anaesthesia is the administration of agents with analgesic and/or anaesthetic properties into the epidural space, whereas "*spinal*" (or subarachnoid or intrathecal) anaesthesia involves administration of the drug into the subarachnoid space (Fig.18). Both techniques have been used for many years in order to achieve high effective anaesthesia and analgesia in pets.

Figure 18.

Fig. 18. *Cross-sectional anatomy of the spinal cord.*



Among neuroaxial techniques, epidural administration of analgesics is traditionally regarded as safer and easier to perform than the spinal route. Owing to its popularity, practicality and ease of performance, single epidural injection is usually preferred to constant rate infusion of analgesics via this route, which can only be accomplished after insertion of an epidural catheter. Placing an epidural catheter is a time-consuming procedure, which requires a certain degree of expertise and also carries the risk of complications (Ladha et al. 2013; Pumberger et al. 2013). Nevertheless, single epidural injections may provide analgesia of insufficient duration when invasive and potentially long surgeries are performed.

The nerve root is the main site of action for local anaesthetics that are injected epidurally. The local anaesthetics diffuse along a concentration gradient through the different nerve structures bathing and blocking the spinal roots (Liu and Bernards 2002; Bernards et al. 2003a,b). In order to achieve sensory and motor block of the entire pelvic limb, the volume of local anaesthetics must be sufficient to cover the lumbosacral plexus (from L3 to S1). The injected volume of local anaesthetics, indeed, involves the cranial migration of the epidural solution. When drugs are injected at L7-S1 space, they migrate in all directions (caudally, cranially, and laterally) within the vertebral canal.

The spread of epidural solutions are affected by numerous factors such as volume and concentration of drug (Lee et al. 2004a; Duke et al. 2000), speed and pressure during injection (Iff et al. 2007), site of injection (Visser et al. 2008), position of the animal (Gorgi et al. 2006), size and permeability of the intervertebral foramina (Bromage 1962), amount of fat in the epidural space (Lee et al. 2004b; Lundblad et al. 2011), size of the associated venous and lymphatic plexus (Park et al. 1980), age and physical condition (Bromage 1962), and baricity and specific gravity of the injected solution.

In small animals, the main indication for epidural injection is to provide analgesia for surgery of the pelvis, pelvic limbs, perineal procedures, and some caudal abdominal procedures; but it can be used to provide anaesthesia and analgesia for any surgical, medical, or diagnostic procedures caudal to the patient's umbilicus. Additionally, this technique can be used successfully in postoperative pain management whether as single injection or epidural catheter (Pascoe and Dyson 1993; Troncy et al. 2002).

Epidural injection is contraindicated in case of thrombocytopenia and coagulation disorders and it should be avoided in animals with clinical bleeding disorders because of their increased risk of haemorrhage. Epidural administration of local anaesthetics should be avoid in patients with hypovolemia and hypotension as well. Local anaesthetics block not only pain and motor fibers, but also sympathetic fibers increasing the risk of hypotension. Other analgesic protocols should be considered in animals with infections or neoplasia at the site of injection in order not to spread infection or tumor cells into the vertebral canal. Epidural anaesthesia should be avoided in pets with neurologic deficits in the area to be blocked. Congenital or traumatic anatomic abnormalities may represent a relative contraindication for increased technical difficulty.

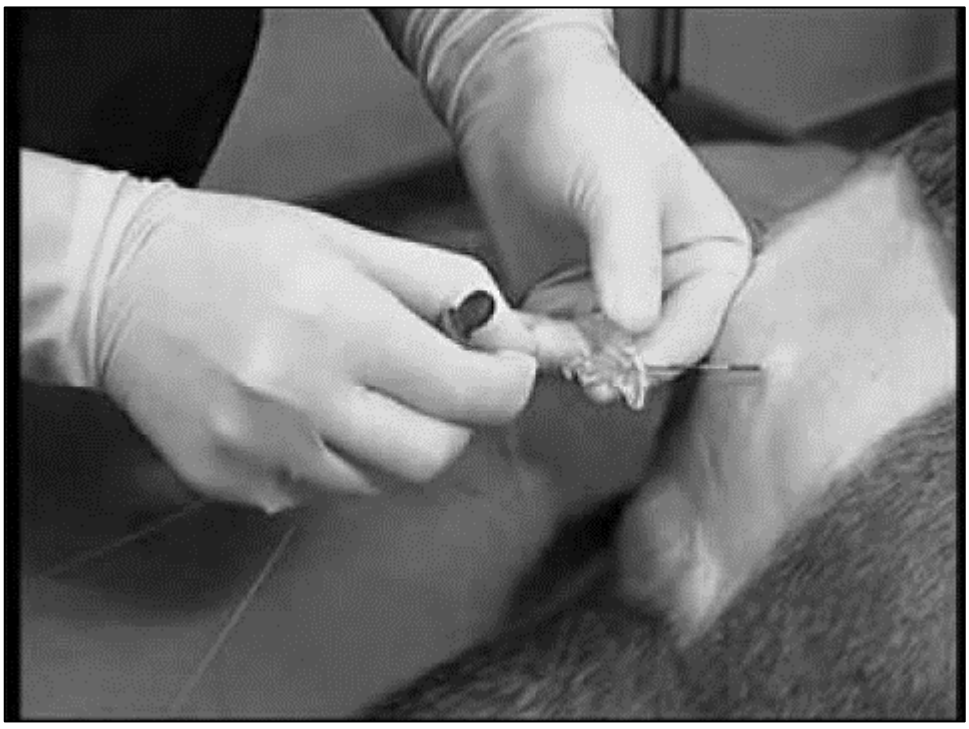
In order to easily perform epidural injection, the patient should be placed in either sternal or lateral recumbency. The quality of the block is improved by standardized positioning, as well as the risk of complications is minimized. The sternal recumbency (with the pelvic limbs pulled forward to open the lumbosacral space) is mostly preferred for L7-S1 epidural injection because it is often easy to detect anatomic landmarks. Besides, it has been shown that the cranial migration is minor than for lateral positioning (Gorgi et al. 2006). Among several methods for locating the epidural space loss of resistance, hanging drop technique, and electrolocation are the most common. The *hanging drop technique* consists in placing a drop of saline in the hub of the needle. As the needle penetrates the epidural space the drop will be usually aspirated into the space due to the subatmospheric pressure within the

vertebral canal. This method is reliable only in sternal positioning (Naganobu and Hagio 2007) and it is useful especially in large breed dogs.

Due to its ease, *lumbosacral epidural anaesthesia* (Fig.19) is the most popular approach performed for cats and dogs. In this technique the injection is placed between the spinous processes of L7 and S1 (medial sacral crest) on the dorsal midline of the animal. The needle is perpendicular to the skin on the dorsal midline, caudal to the spinous process of L7. As the needle penetrates the skin and the subcutaneous tissue, usually there is not resistance. When the needle is slowly advanced through the interspinous ligament the anaesthetist feels resistance. The needle is then advanced until a sudden loss of resistance is appreciated and the needle enters the extradural space. Once the epidural space is correctly determined, injection of the solution can be slowly (1-2 minutes) performed. Adverse effects, namely irregular blockade or cranial migration of the anaesthetic solution, may be caused by a fast injection. It is recommended to observe potential side effects (pain, tachycardia, hypotension, arrhythmias, muscle twitches, tremors, or seizures) during and after injection. No resistance to injection into the epidural space should be shown, otherwise nervous tissue may be damaged (Torske and Dyson, 2000).

Figure 19.

Fig. 19. *Lumbosacral epidural anaesthesia approach.*



Body weight and spinal length are useful to calculate the volume of epidural solution. According to the *body weight* method, 0.2 $mLkg^{-1}$ (1 mL $5kg^{-1}$) total final volume is the recommended dose to determine block up to L1. Lower volumes (1 mL $7kg^{-1}$) are required for surgery involving the pelvic limbs and even lower doses for tail and perineal area (1 mL $10kg^{-1}$). In the s*pinal length* method, total vertebral column length (LOC) is defined as centimeters measured between the occipital condyle and the first coccygeal vertebra. Given the relantionship between cranial migration of solutions administered in the extradural space and the LOC, the volume of anesthetic solution can be calculated in dogs with abnormal spinal lengths or in obese animals. The epidural anaesthetic volume is calculated as mLcm LOC^{-1}: 0.05 mLcm LOC^{-1} will block 30-35% of the LOC; 0.1 mLcm LOC^{-1} will block 55-60% of the LOC; 0.15 mLcm LOC^{-1} will block 70-75% of the LOC (Otero et al. 2009).

Several types of agents can be administered via epidural route in small animal practice. Commonly, local anaesthetics, opioids, and α2-agonists, or combinations of these drugs are given epidurally. The desired action (sensory only vs. sensory and motor blockade) and the desired duration of action influence the choice of drug combination. Many factors determine the duration of nerve blockade. First, the type of local anaesthetic (short as 4.4 mg kg^{-1} lidocaine 2% with 120 minutes of duration; intermediate as 0.14 mg kg^{-1} bupivacaine 0.75% with 160 minutes; long as 1 mg kg^{-1} levobupivacaine 0.75% with 360 minutes) (Cruz et al. 1997; Gomez de Segura et al. 2009). Second, concentration and volume given: the higher they are the longer the block is (Duke 2000; Gomez de Segura et al. 2009; Freire et al. 2010). Third, lipid solubility (Bernards 2004); systemic absorption through the epidural vascular network (Emanuelsson et al. 1997) and binding to nerve cell proteins. Last, local vasodilator/vasoconstrictor effects of each agent (ropivacaine is the only local anaesthetic with intrinsic vasoconstrictor effect) (Nakamura et al.1993) and addition of epinephrine which decreases vascular absorption (this effect is less evident with ropivacaine and other long acting agents) (Duke et al. 2000).

PAIN ASSESSMENT

During last twenty years, prevention, assessment and treatment of pain have been gained more and more interest in veterinary medicine.

It has been shown not only that animals feel and anticipate pain by similar mechanisms as people (Vierck 1976), but also that pain worsens the healing process and the well-being of any animal (Morton and Griffiths 1985; Smith et al. 1996). Painful experience often involves prolonged hospital staying and potential secondary problems (immune suppression, secondary illness, inappetence, and cachexia).

Considering all the negative physiologic effects associated with the experience of pain, above all, ethical considerations must be taken in order to avoid the inhumane aspects of this unnecessary experience.

Assessment is the first step in management of pain, but it can be very challenging in veterinary medicine. Assessment is often based on evaluation of behavioural and physiologic characteristics that are present when there is acute pain (Appendix 1) (Morton et al. 1985; Mathews et al. 1996; Smith et al. 1996; Crane 1987; Hansen 1997; Hansen et al. 1997; Hardie et al. 1997; Haskins 1987; Mathews 1998).

An anthropomorphic approach to management of pain should be used if the caregiver has difficulty in interpreting the behavioural characteristics associated with a situation known to cause pain. In human patients, the “gold standard” for pain assessment and its relief is verbal communication with the patient; unfortunately, this is not possible in veterinary medicine. The evaluation must be tailored for each patient based on the age and the breed of the animal. Younger animals and toy and small breeds are much less tolerant of pain than eldery animals and large breed dogs.

Appendix 1.

Appendix 1. *Behviorural characteristics associated with pain in cats and dogs. These signs are not consistently in painful states and some may be present in any anxious or excited animal.*

- Abnormal posture:
  - hunched up guarding or splinting of abdomen
  - “praying” position
  - sitting or lying in an abnormal position
  - not resting in a normal position
- Abnormal gait:
  - stiff
  - no to partial weight bearing on injured limb
  - slight to obvious limp
- Abnormal movement:
  - thrashing
  - restless
  - no movement when not sleeping
- Vocalization:
  - screaming
  - whining
  - crying
  - none
- Miscellaneous:
  - looking, licking, or chewing at the painful area
  - hyperesthesia or hyperalgesia
  - allodynia
- Behavioural characteristics associated with pain, but may also be associated with poor general health (mediacl problems):
  - restless or agitated
  - trembling or shaking
  - tachypnea or painting
  - weak tail wag
  - low carriage of tail
  - depressed or poor response to caregiver
  - head hangs down
  - not grooming
  - appetite decreased, picky, or absent
  - dull

- lying quietly and not moving for hours and does not dream
- stuporous
- urinates or defecates and makes no attempt to move
- recumbent and unaware of surroundings
- unwilling or unable to walk
- bites or attempts to bite caregivers

- May also be associated with apprehension or anxiety:
  - restless or agited
  - trembling or shaking
  - tachypnea or painting
  - weak tail wag
  - low tail carriage
  - slow to rise
  - depressed (poor response to caregivers)
  - not grooming
  - bites or attempts to bite caregiver
  - ears pulled back
  - restless
  - barking or growling
  - growling or hissing
  - sitting in the back of the cage or hiding under a blanket (cat)
- May be normal behaviour:
  - reluctant to move head (eye movement only)
  - stretching all four legs when abdomen touched
  - penile prolapse
  - cleaning (licking) a wound or incision
- Physiologic signs that can be associated with pain:
  - tachypnea or painting
  - tachycardia
  - dilated pupils
  - hypertension
- increased serum cortisol and epinephrine

A number of different pain scales have been developed for use, most adapted from those for human medicine. A key difference between human and veterinary pain scales is in veterinary medicine all are based on observer interpretation of the intensity of the animal's pain.

For maximal patient benefit, it is crucial only one pain scale is used throughout treatment. This allows assessment of the patient's response to analgesic therapy and can guide future treatment. Changing between types of pain scales for individual patients is not advised, as the variation will prevent temporal comparison.

In human medicine there are numerous ways to assess pain and a few have been used in animals. None are perfect, primarily because pain is subjective and unmeasurable even in human beings (Hamill-Ruth et al. 1999) and especially in veterinary medicine where patients can not communicate verbally. Pain assessment in non-verbal species can be complicated by external factors. The presence of environmental or situational stressors can modulate the patient's response to pain. Administration of sedative drugs as part of a perianaesthetic protocol may mask behavioural changes associated with pain. In humans, the pain response can be amplified by anxiety, causing hyperalgesia (Colloca and Benedetti 2007).

Using standardised pain scales allows a repeatable measure that is consistent between observers. Additionally, if the pain score is recorded over time, it allows an objective evaluation of a patient's response to management.

There are many different pain scoring or assessment systems in veterinary medicine: *verbal rating scales* (VRSs) or *simple descriptive scales* (SDSs), numeric rating scales (NRSs), and *visual analogue scale* (VAS) (Taylor and Houlton 1984; Popilskis et al. 1991; Waterman and Kalthum 1992; Conzemius et al. 1994; Day et al. 1995; Mathews et al. 1996; Lascelles et al. 1997; Slingsby and Waterman-Pearson 1998; Griseaux et al. 1999) (Fig.13). All these scales are affected by variability among observers and are designed to assess acute pain.

The VRSs and SDSs are very simple as they are characterized by only four pain scores (none, mild, moderate and severe), but they seem to lack sensitivity. Few levels might not provide sufficient discrimination from one level to the next (Richard-Hibon et al. 1999).

The VAS is a ruler (usually 100 mm long) with a description of the limits of pain placed at either end of the scale such that 0 represents no pain and 100 represents the worst pain possible. The observer is asked to mark anywhere along the scale where the perceived pain would fall. The perception of the animal's pain can be quantified by measuring the distance

in millimetres from zero. Arbitrary cut-off values can be set for determining analgesia administration. Studies in human medicine suggest values lower than 35mm are consistent with mild pain, while above this value pain becomes progressively more severe (Boonstra et al. 2014). Regular, repeated assessment and recording of values allows response to analgesia to be determined. This scale is very common not only in human medicine but also in veterinary medicine (Waterman and Kalthum 1992; Lascelles et al. 1997; Slingsby and Waterman-Pearson 1998). It has been shown that the VAS is sensitive, reproducible, and feasible (Jensen et al. 1986) when the observer is experienced in assessing pain and trained in the use of the scale.

Dynamic interactive visual analogue scale (DIVAS) is an expanded version of the VAS. It uses the same principle of marking the perceived pain level along a 100mm line. However, DIVAS also relies on the handler interacting with the patient and gently palpating surgical wounds to provide a complete score.

Numerical rating scales (NRSs) are comparable to VAS, with similar caveats, although the scale is drawn with discrete numbers, from zero to 10, on the illustrated line (Figure 20). As with a VAS scale, zero represents no pain and 10 represents the worst pain imaginable. Such a system may have a reduced sensitivity compared to VAS, as only whole integers are used.

Figure 20.

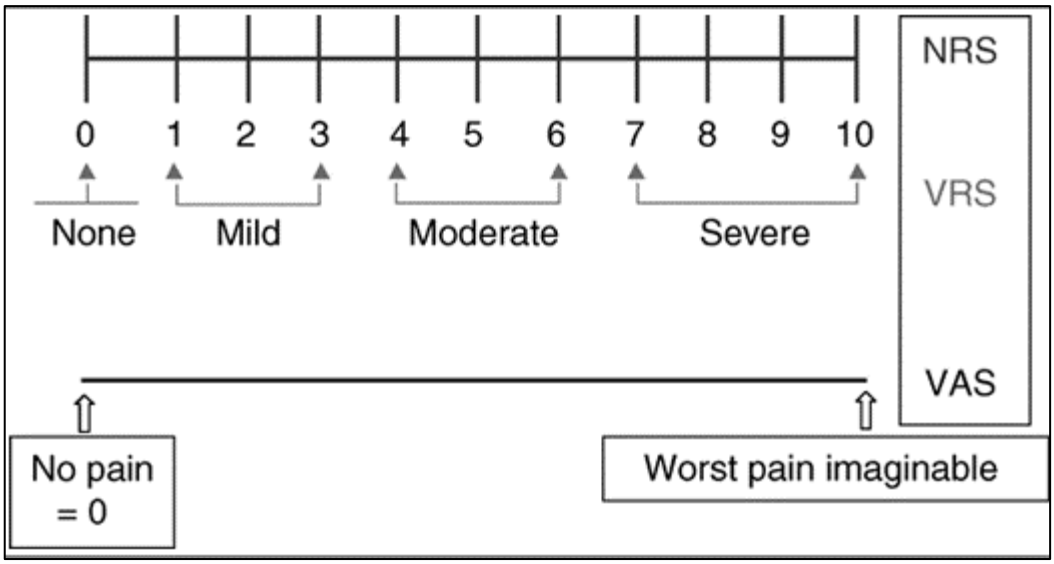


Fig. 20. *Different pain scoring or assessment systems in veterinary medicine: verbal rating scales (VRSs) or simple descriptive scales (SDSs), numeric rating scales (NRSs), and visual analogue scale (VAS)*

VAS and NRS are considered unidimensional, as they only assess pain intensity. However, as it is shown in appendix 1, pain affects an animal in multiple ways; therefore, multidimensional composite scales have been developed to incorporate such factors, assessing not only the physical pain intensity, but also emotional effects. Such scales often weigh behaviours and variables differently, which may help to minimise the interobserver variability seen with more basic scales. Some multidimensional composite pain scales take account of both physiological and behavioural aspects while some focus primarily on behavioural changes, usually with and without handler interaction. As with other pain scales, these rely on user experience of normal behaviour for the particular species.

The short form of the Glasgow composite measure pain scale (Morton et al. 2005) (Appendix 2) for canine acute pain is probably the best known multidimensional pain scale. This was preceded by *the University of Melbourne's pain scale* (Firth and Haldane, 1999) (Appendix 3).

Appendix 2.

Appendix 2. *The short form of the Glasgow composite pain scale. Validated for assessment of acute pain associated with multiple conditions in dogs through a questionnaire completed by veterinary personnel.*

SHORT FORM OF THE GLASGOW COMPOSITE PAIN SCALE

Dog's name _____

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

Surgery Yes/No (delete as appropriate)

Procedure or Condition_____

_____

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

A. Look at dog in Kennel

Is the dog?

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

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

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

When the dog rises/walks is it?

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

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

Does it?

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

D. Overall

Is the dog?

(v)	
Happy and content or happy and bouncy	0
Quiet	1
Indifferent or non-responsive to surroundings	2
Nervous or anxious or fearful	3
Depressed or non-responsive to stimulation	4

Is the dog?

(vi)	
Comfortable	0
Unsettled	1
Restless	2
Hunched or tense	3
Rigid	4

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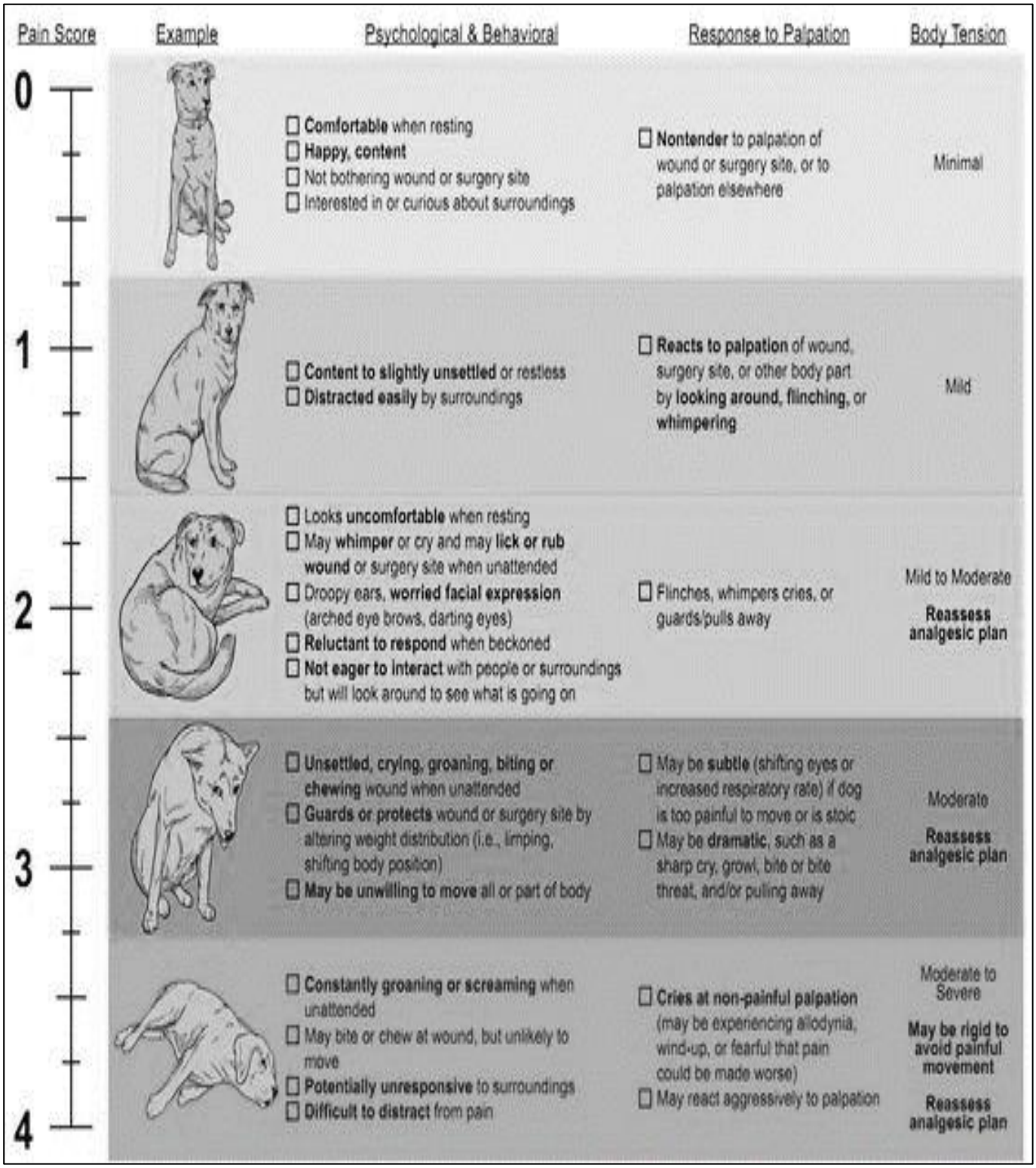
Total Score (i+ii+iii+iv+v+vi) = _____

Appendix 3.

Appendix 3. *The University of Melbourne's pain scale.*



The pathophysiology of acute and chronic pain differs greatly. Acute pain is generally caused by injury and often serves a protective or biological purpose. It is usually self-limiting and associated with the timescale of normal healing. Chronic pain, however, is often considered a disease state in its own right, doesn't serve any biological purpose and has no recognisable end point (Grichnik and Ferrante 1991).

Both the nature of the two pain states and their behavioural indicators are different. Therefore, pain scales designed for acute or chronic pain are not interchangeable. Acute pain scales are often designed for use by veterinary personnel in a hospital environment, as this is where acute pain is most likely to be experienced. Although it is always beneficial to know the pain-free behaviour of the animal, it is possible for a naïve observer/handler who has knowledge of the general species' behaviour to use an acute pain scale to judge the level of pain.

In contrast, behavioural changes associated with chronic pain can often be subtle and gradual in onset. As a result, such alterations can only be recognised by someone who is very familiar with the animal, usually the owner (Mathews et al. 2014). However, sometimes owners are unaware subtle changes may be associated with pain and often it is only highlighted when there is an improvement in patient demeanour during an analgesia trial.

Chronic pain scales revolve around quality of life questionnaires and functional assessment of the animal. Factors considered often include:

- mobility
- daily activity levels
- interest in food and water
- grooming
- behaviour changes in temperament and demeanour (Brown et al. 2007; Hielm-Björkman et al. 2009; Mathews et al. 2014).

For chronic pain associated with osteoarthritis, *Liverpool osteoarthritis in dogs scale* (Hercock et al. 2009; Walton et al. 2013), *Canine brief pain inventory* (Brown et al. 2007; Brown et al. 2008; PennVet. 2006), and *Helsinki chronic pain index (*HCPI; Hielm-Björkman et al. 2009; University of Helsinki (2012) are validated scales through the use of owner questionnaires . The HCPI also uses a questionnaire completed by the veterinary surgeon.

In conclusion, assessing pain in veterinary species can be challenging. Pre-existing knowledge of normal speciesspecific behaviour is essential. Pain scales enable a more objective assessment of pain and allow serial assessments to be compared.

Regular, repeated assessments with the same scale are required to determine if there has been a positive response to analgesia provision and to guide further therapy. Use of appropriate pain scales can help improve animal welfare in an acute, postoperative setting and animal quality of life during chronic pain states.

RESEARCH STUDY

AIM OF THE STUDY

The aim of this study was to determine whether the addition of magnesium sulphate to epidural ropivacaine would result in better peri-operative analgesia - in terms of longer duration and decreased need for rescue analgesics - than ropivacaine alone, in client-owned dogs anaesthetised for elective hip arthroplasty.

Our hypothesis was that the addition of magnesium to ropivacaine would improve peri-operative analgesia, without prolonging the motor block or causing neurological dysfunction of the hind limbs.

MATERIALS and METHODS

Animals

Twenty client-owned dogs scheduled for hip arthroplasty between March 2014 and February 2016 were involved in this study. All dogs underwent a pre-anaesthetic physical examination and a complete blood test, including haematology and biochemistry, was carried out to rule out abnormalities. Exclusion criteria were ASA (American Society of Anaesthesiologists) risk category higher than II and skin infections at the level of the lumbosacral area. The clinical trial was performed with permission of the Ethical Committee of the Veterinary Teaching Hospital of the University of Turin (Italy), and written consent signed by the dogs'owners.

Study design

This clinical study was designed as an investigator-blind, controlled, randomized, prospective trial. A block randomization method was used in order to allocate the dogs to one of two treatment groups. Briefly, an operator not participating to the assessments was in charge for keeping an opaque, sealed envelope from which treatment assignments were shuffled and drawn. This same operator was also responsible for the allocations' list until

the end of data collection. The number of dogs per group was determined on the basis of a sample size calculation. Each group was to be composed of a minimum of 10 dogs in order to detect, with one-way analysis of variance (with power equal to 0. 95% level of confidence and α value and standard deviation set at 0.05 and 40 minutes, respectively), a difference between groups in the mean duration of analgesia (defined as the time from the epidural injection to the administration of the first dose of rescue analgesic agent) equal to at least 60 minutes.

Anaesthetic protocol and procedures

All dogs were premedicated with intramuscular (IM) acepromazine (0,03 mg kg^{-1}, Prequillan; Fatro, Italy). Thereafter, intravenous (IV) propofol (Vetofol; Esteve, Spain) was titrated to effect to induce general anaesthesia. After orotracheal intubation, isoflurane (Isoflo; Esteve, Spain) was delivered in oxygen via a circle system and lactated Ringer's solution was perfused IV (10 mL kg^{-1} hr^{-1}, Ringer Lattato; Fresenius Kabi, Italy). Arterial blood pressure (systolic: SAP; mean: MAP and diastolic: DAP) was continuously measured through an indwelling catheter placed in the dorsal pedal artery. Monitoring during anaesthesia included both cardiovascular (SAP, MAP, DAP, heart rate [HR] and rhythm) and respiratory (end tidal carbon dioxide [$P_{E'}CO_2$], peak inspiratory pressure [PIP], respiratory rate [f_R], tidal volume [V_T], minute volume [V_E], inspired fraction of oxygen [FiO_2], end tidal isoflurane tension [$P_{E'ISO}$]) parameters, as well as oesophageal temperature (T°,C). Manual data recording was performed every 5 minutes for the entire duration of anaesthesia. Spontaneous breathing was preferred unless $P_{E'}CO_2$ reached more than 45 mmHg; in that case mechanical ventilation was used to maintain normocapnia. During anaesthesia the target was a constant $P_{E'ISO}$ of 1.3%, which is equal to the Minimum Alveolar Concentration (MAC) as determined in dogs (Valverde et al. 2003; Barletta et al. 2016).

A bolus of IV atropine (0.01 mg kg^{-1}, Atropina Solfato; ATI, Italy) was injected when bradycardia (<45 beats per min [BPM]) occurred. Treatment of hypotension (MAP <60 mmHg) consisted of an IV bolus of lactated Ringer's solution (10 mg kg^{-1} over 10 min), followed by an IV colloid bolus (Voluven; Fresenius Kabi, Italy; 2 mL kg^{-1} over 10 minutes), and then by an IV infusion of dopamine (Revivan; AstraZeneca, Italy; starting at 10 µg kg^{-1} min^{-1}, to be incremented by 2.5 µg kg^{-1} min^{-1} every 10 min until MAP increased above 60 mmHg) in the event of unresponsive hypotension. Bradyarrhythmias and hypotension occurring shortly after the epidural injection were regarded as clinical symptoms compatible

with hypermagnesaemia or sympathetic nerve blockade and their occurrence was recorded. The duration of surgery and of anaesthesia (minutes) were recorded. The time elapsed from termination of inhalational anaesthesia to recovery to intensive care unit (minutes) was defined as "time to recovery", and recorded. The trachea was extubated after return of swallowing and palpebral reflexes, accompanied by increased jaw tone; at this point, all dogs were administered with IV carprofen (4 mg kg-1, Rimadyl; Pfizer, Italy).

Epidural injection

As soon as the anaesthesia plane was deemed surgical based on classical clinical parameters (relaxation of the jaw, absence of blinking and movements, light palpebral reflex and physiological parameters within normal interval limits for dogs) the anaesthesist (Elena Lardone), who was blinded to the treatment, performed all the epidural injections. The dogs were positioned in sternal recumbency with the hind limbs cranial symmetrically in order to maximize the dorsal lumbosacral space. The ilium wings, together with the sacrum and the dorsal spinous processes of L6 and L7, were used as anatomical landmarks. After surgical preparation of the area, a 75 mm, 19 gauge spinal needle (BD, Italy) was inserted percutaneously between L7 and S1, with the bevel facing cranial, and then advanced through the intervertebral ligament into the epidural space. Both the "popping" sensation, perceived while penetrating the interarcuate ligament, and the hanging drop technique with saline were used for a first assessment of proper needle placement. Radiographic exam followed to confirm correct positioning of the needle between L7 and S1. After the epidural injection was performed, sternal recumbency was kept for a few minutes.

Treatment groups

Epidural ropivacaine (Naropina 0.5%; AstraZeneca, Italy), 1 mg kg^{-1} (volume: 0.2 mL kg^{-1}), was administered epidurally to group C (Control), while group M (Magnesium) was treated with ropivacaine (1 mg kg^{-1}; volume: 0.2 mL kg^{-1}) and magnesium sulfate (Magnesio Solfato 2g $10mL^{-1}$; Galenica Senese, Italy) at the dose of 2 mg kg^{-1} (volume: 0.01 mL kg^{-1}). The drugs were mixed in the same syringe and given as a single bolus over 1 minute. Doses were chosen on the basis of the authors' past clinical experience, and of human and veterinary medicine literature (Arcioni et al. 2007; Bilir et al. 2007; Oezalevli et al. 2005).

Assessment of intra-operative nociception and post-operative pain

Intraoperative nociception was defined as an increase in HR, MAP and/or f_R of at least 20% compared to the baseline (recorded before skin incision, after $P_{E'ISO}$ had been maintained constant at 1.3% for at least three consecutive measurements, over 15 min). When two of these three parameters increased above the defined values, rescue fentanyl (Fentanest; Pfizer, Italy) was administered IV (0.003 mg kg^{-1}).

Postoperatively, a multifactorial pain score modified from Sammarco ranging from 0) no pain to 13) extreme pain (Appendix 4; Sammarco et al. 1996; Adami et al. 2012) and the short form of the Glasgow pain scale ranging from 0) no pain to 20) extreme pain (Holton et al. 2001) were used to evaluate pain (Appendix 2). Additionally, a 10 cm visual analogue scale (VAS) with end points labelled 0) worst possible pain to 10) absence of pain was utilized. Rescue analgesia consisted of 0.01 mg kg-1 buprenorphine IV (Temgesic; Schering Plough, UK), administered when at least one pain score was 40% or more of the maximum value of the scale (<6 for the VAS, >5 for the multifactorial pain score scale, >8 for the Glasgow pain scale).

A modified Tarlov's scale (Appendix 5) ranging from 0) neurological impairment to 4) no signs of motor block (Buvanendran et al. 2002; Adami et al. 2016) was used for neurological assessment of the hind limbs and quantification of motor blockade. The same observer (Elena Lardone), who was unaware of the treatment, performed all the evaluations. All dogs were evaluated when deemed awake enough to respond to vocal call and incitement to sit or stand up, and then 60, 120, 180, 240, 300 minutes and 24 hours after end of surgery and before being discharged from the hospital.

Appendix 4.

Appendix 4. *Modified multifactorial pain score (Sammarco et.al., 1996; Adami et al., 2012) to assess post-operative pain in 20 dogs undergoing total hip replacement. The same observer who was blind to the treatment evaluated the dogs as soon as they were awake enough to respond to stimulation (vocal call and incitement to sit or stand up) and then 60, 120, 180, 240, 300 minutes and 24 hours after surgery.*

Vocalization								
-None	0	0	0	0	0	0	0	0
-Intermittent vocalization	1	1	1	1	1	1	1	1
-Continuous vocalization	2	2	2	2	2	2	2	2
Movement								
-None	0	0	0	0	0	0	0	0
-Frequent position changes	1	1	1	1	1	1	1	1
- Rolling, thrashing	2	2	2	2	2	2	2	2
Agitation								
-Calm	0	0	0	0	0	0	0	0
-Mild agitation	1	1	1	1	1	1	1	1
-Moderate agitation	2	2	2	2	2	2	2	2
-Severe agitation	3	3	3	3	3	3	3	3
Heart rate								
-1-15% above pre-operative value	0	0	0	0	0	0	0	0
-16-29% above pre-operative value	1	1	1	1	1	1	1	1
-30-45% above pre-operative value	2	2	2	2	2	2	2	2
->45% above pre-operative value	3	3	3	3	3	3	3	3
Respiratory rate								
-1-15% above pre-operative value	0	0	0	0	0	0	0	0
-16-29% above pre-operative value	1	1	1	1	1	1	1	1
-30-45% above pre-operative value	2	2	2	2	2	2	2	2
->45% above pre-operative value	3	3	3	3	3	3	3	3
Total (0-13)								

Appendix 5.

Appendix 5. *Modified Tarlov's scale (Buvanendran et al., 2002; Adami et al., 2016) to evaluate the neurological function of the hind limbs and the degree of motor blockade in 20 dogs undergoing total hip replacement. The same observer who was blind to the treatment evaluated the dogs as soon as they were awake enough to respond to stimulation (vocal call and incitement to sit or stand up) and then 60, 120, 180, 240, 300 minutes and 24 hours after surgery.*

Grade 0	Flaccid paraplegia, no movements of the hind limbs, possible loss of bowel/ urinary bladder control
Grade 1	Spastic paraplegia with moderate or vigorous purposeless movements of the hind limbs. No sitting, unable to walk
Grade 2	Good movements of the hind limbs but unable to stand
Grade 3	Able to stand but unable to walk normally; hips and limbs obviously unstable, moderate to severe ataxia
Grade 4	Able to stand and walk normally, some muscle weakness of the hind limbs may be seen

Statistics

Statistical analysis was accomplished with commercially available software (SigmaStat and SigmaPlot 12, Systat Software Inc.). Normality of data distribution was assessed with the Kolmogorov-Smirnov test and with the Shapiro-Wilk test. Following, continuous variables were analysed with either one way repeated measures analysis of variance followed by Holm-Sidak method for multiple comparison, or Friedman repeated measures analysis of variance on ranks followed by Tukey test, where it applied. For the analysis of intra-operative cardiovascular and respiratory variables, only the values recorded during three significant events were used: before surgery (baseline as above described: 0), 30 seconds after skin incision (1), and during femoral head osteotomy (2).

For non-continuous variables, either T-test or Mann Whitney Rank Sum test were used. Within each treatment group, the proportions of dogs which experienced hypotension and bradyarrhythmias following epidural injection of magnesium were analysed with the Fisher exact test. P values < 0.05 were considered statistically significant.

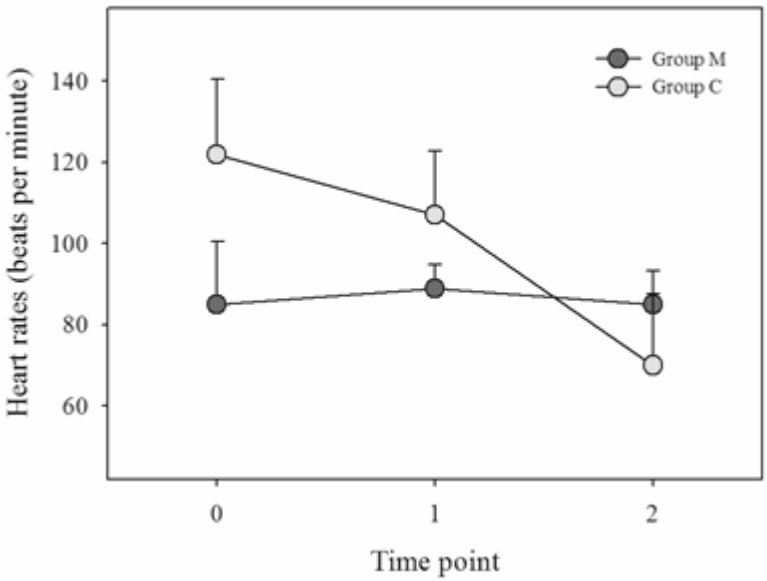
RESULTS

Data are presented as either means ± SD or medians [25%-75% ranges].

Twenty dogs of any breed (12 female and 8 male) 9 months to 12 years of age entered and completed this study.

Heart rate, MAP, time to recovery and duration of anaesthesia were normally distributed. Anaesthesia was uneventful in all dogs enrolled in the study and lasted 222 ± 62 minutes in group M and 220 ± 32 minutes in group C, respectively; this difference was not statistically significant. The treatment groups did not differ with respect to intra-operative physiological variables (Figure 21). However, HR decreased over time in the control group, while MAP increased in both treatment groups. Respiratory rate increased over time in group M while it decreased in group C. Cardiovascular events compatible with hypermagnesaemia, namely bradyarrhythmias and hypotension, were not observed during the anaesthetics.

Figure 21.



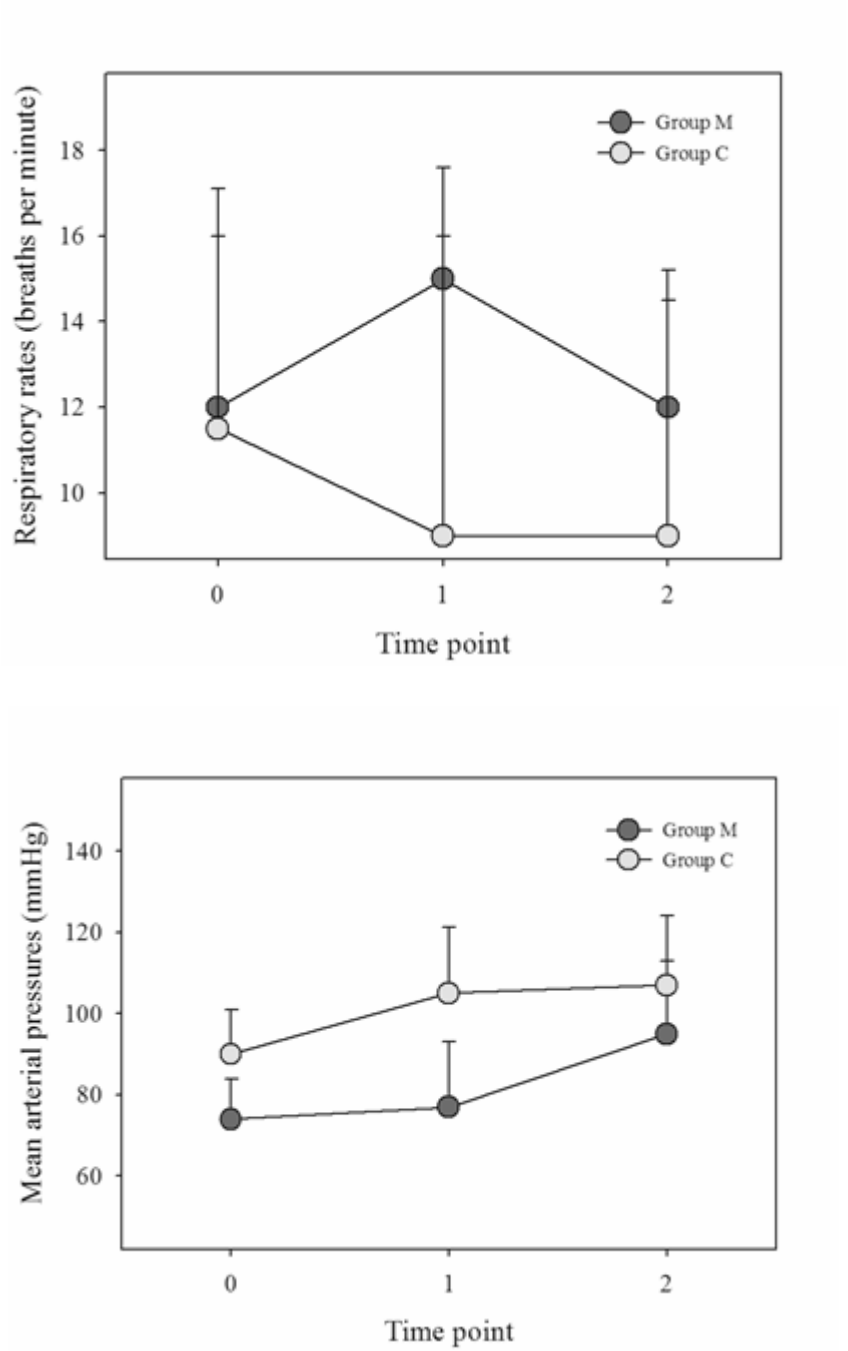
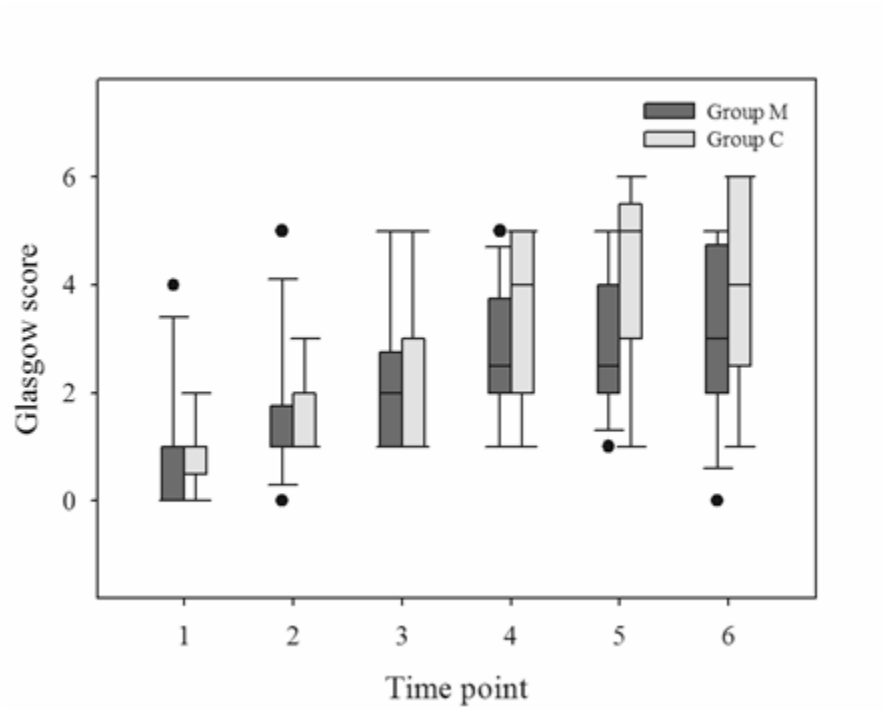


Fig.21. *Intra-operative physiological variables recorded from 20 dogs anaesthetized for THR and assigned to one of two treatment groups: group C (Control, received epidural ropivacaine; n=10) and group M (Magnesium, received an epidural combination of magnesium and ropivacaine; n=10). 0: values recorded as baseline in the anaesthetized dogs prior to surgical stimulation; 1: values recorded immediately after skin incision; 2: values recorded after femoral head osteotomy; *: statistically significant difference between time points and the baseline.*

Three dogs of group M (0[0-1]) and 4 of group C (0[0-2]) needed boluses of rescue fentanyl during surgery. This difference was not statistically significant. No difference in duration of surgery, which lasted 120 [90-120] and 125 [120-150] minutes in groups M and C, respectively, was detected between groups. Only one dog, assigned to the control group, before completion of pain assessments needed rescue buprenorphine according to Sammarco and VAS scores (respectively, 7 and 6.8).

The control group achieved lower VAS scores (9.2[7.5-10] versus 9.5[7.9-10]) and higher Sammarco and Glasgow scores (1[0-3] versus 1[0-2.75] and 2[1-3] versus 1[1-4], respectively) than group M at the majority of the time points, however these differences were not statistically significant (Figure 22; Table 1).

Figure 22.



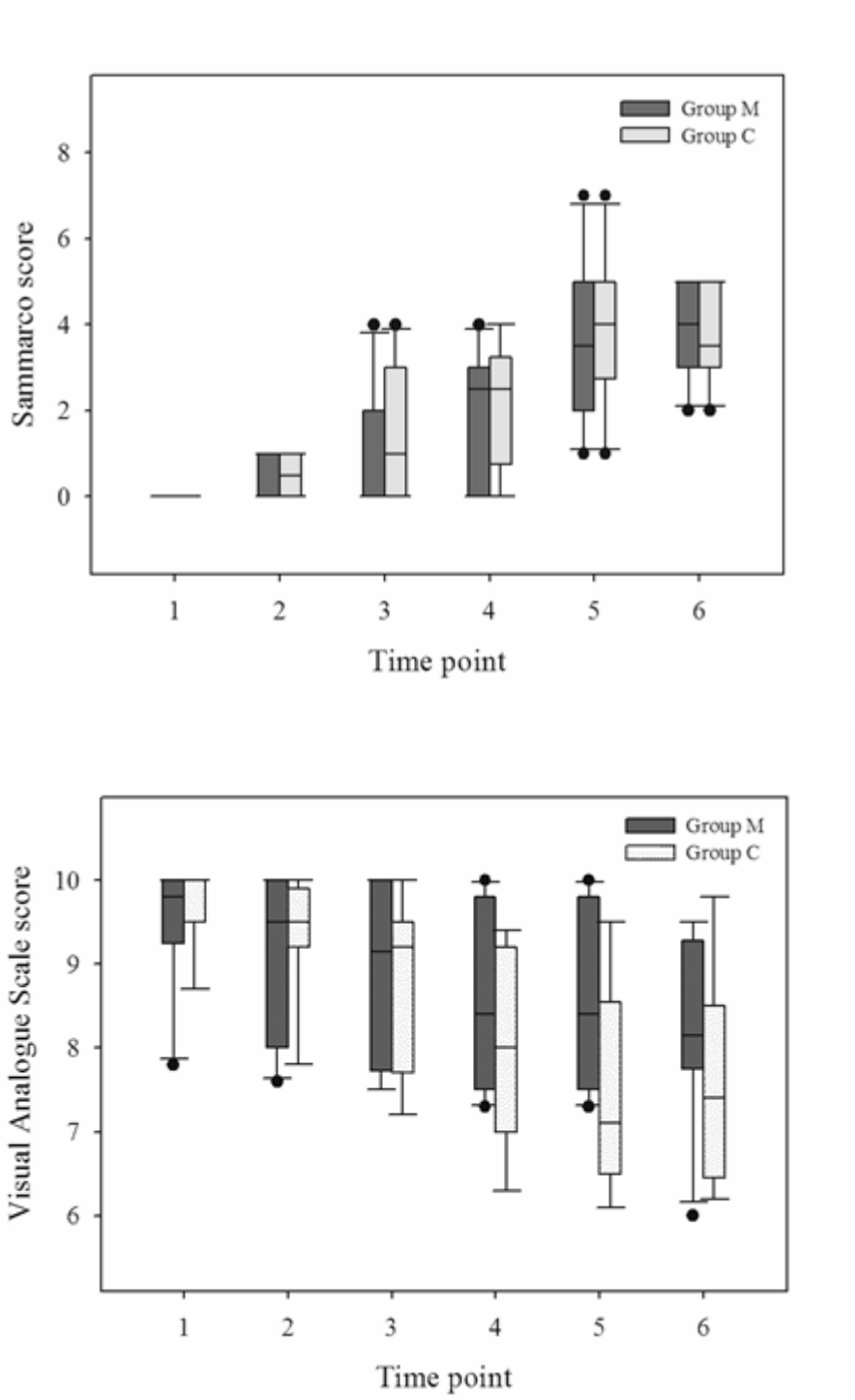


Fig.22 *Post-operative pain scores recorded from 20 dogs anaesthetized for THR and assigned to one of two treatment groups: group C (Control, received epidural ropivacaine; n=10) and group M (Magnesium, received an epidural combination of magnesium and ropivacaine; n=10). 1: values recorded after recovery, as soon as the patients were able to sit and respond to vocal call; 2, 3, 4, 5 and 6 are 60, 120, 180, 240, 300 minutes and 24 hours after recovery; *: statistically significant difference between time points and the baseline.*

Table 1

P and q values of intra-operative and post-operative variables recorded from 20 dogs undergoing hip arthroplasty and assigned to either group C (Control, received epidural ropivacaine; n=10 dogs) or group M (Magnesium, received an epidural combination of magnesium and ropivacaine; n=10 dogs). NA: not applicable.

VARIABLE	**P value**	**q value**
DURATION OF ANAESTHESIA		
Group M versus Group C	0.87	NA
REQUIREMENT OF RESCUE FENTANYL		
Group M versus Group C	0.42	NA
DURATION OF SURGERY		
Group M versus Group C	0.19	NA
HEART RATE		
Group M versus Group C	0.050	NA
Group M versus time	0.025	NA
Group C versus time	0.017	NA
MEAN ARTERIAL PRESSURE		
Group M versus Group C	>0.05	1.10
Group M versus time	<0.05	8.80
Group C versus time	<0.05	7.70
RESPIRATORY RATE		
Group M versus Group C	>0.05	0.36
Group M versus time	<0.05	8.00
Group C versus time	<0.05	8.40
SAMMARCO SCORE		

Group M versus Group C	>0.05	1.00
Group M versus time	<0.05	6.00
Group C versus time	<0.05	5.00
GLASGOW SCORE		
Group M versus Group C	>0.05	3.10
Group M versus time	>0.05	2.80
Group C versus time	>0.05	0.30
VAS SCORE		
Group M versus Group C	>0.05	0.50
Group M versus time	<0.05	12.16
Group C versus time	<0.05	11.65
TARLOV'S SCORE		
Group M versus Group C	>0.05	2.40
Group M versus time	<0.05	6.80
Group C versus time	<0.05	4.60

Group M had lower scores for the Tarlov's scale than group C (2[0-4] versus 3[0-4]) (Fig.23) but this difference was not significant. In both groups the Sammarco, the Glasgow and the Tarlov's scores significantly increased over time, while VAS decreased.

Figure 23.

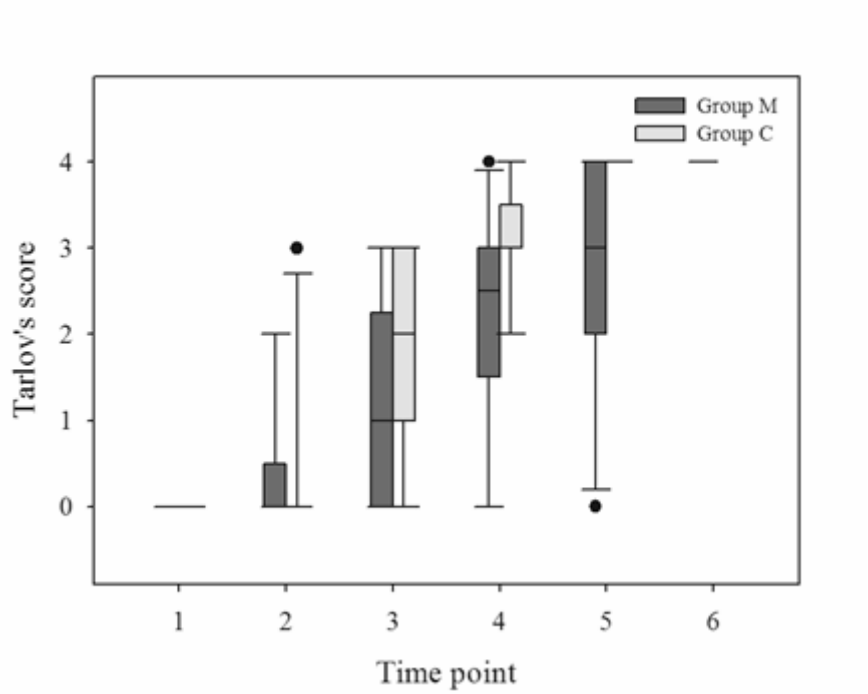


Fig.23 *Tarlov's scores recorded from 20 dogs anaesthetized for THR and assigned to one of two treatment groups: group C (Control, received epidural ropivacaine; n=10) and group M (Magnesium, received an epidural combination of magnesium and ropivacaine; n=10). 1: values recorded after recovery, as soon as the patients were able to sit and respond to vocal call; 2, 3, 4, 5 and 6 are 60, 120, 180, 240, 300 minutes and 24 hours after recovery; *: statistically significant difference between time points and the baseline.*

Recovery was smooth in all the dogs included in the study and normal motor function of the hind limbs was recovered within 6 hours from the epidural injection. Peri-anaesthetic complications were not observed.

DISCUSSION

Although the addition of epidural magnesium to ropivacaine resulted in less rescue analgesics requirement and lower post-operative pain scores and higher VAS compared to ropivacaine alone, we failed to demonstrate a statistically significant difference in terms of quality and duration of analgesia between the two treatments. The duration of the motor block was also comparable between the two groups, and the administration of magnesium was not associated with neurological dysfunction of the hind limbs.

Our findings are in disagreement with those of a previous study, which found that the spinal addition of magnesium to ropivacaine potentiated the intensity and the duration of analgesia in dogs after tibial plateau levelling osteotomy (Adami et al. 2016), but also prolonged the duration of the motor block.

Possible explanations for this discrepancy are less effective analgesia when magnesium is given epidurally compared to the spinal route or, alternatively, a failure in the methods used in the current study to detect a difference between treatments.

Besides the possibility of a direct analgesic effect of magnesium on the dorsal horn NMDA receptors, Adami and colleagues hypothesized that the ionized magnesium released by its salt may exert antinociception also by blocking the calcium currents, which in turn could alter the resting potential of the neuronal membranes (Adami et al. 2016). Alternatively, as a hyperosmolar salt, magnesium sulfate might cause osmotic interference with the cerebrospinal fluid and spinal cord, leading to neuronal shrinking and transient neurologic dysfunction (Busselberg et al. 1994). Both mechanisms are more likely to occur when magnesium is injected spinally rather than via the epidural route, owing to a higher concentration being achieved at the cerebrospinal fluid when the same dose was used spinally and epidurally.

Another reasonable explanation is that the epidural route of administration requires a higher magnesium dose than the spinal one in order to detect appreciable analgesia. Owing to ethical obligations, and not to cause any harm to client-owned dogs, in the current study it was decided to use a dose of magnesium which was proven to be safe in terms of risks for direct neurotoxicity (Simpson et al. 1994) and hypermagnesaemia (Adami et al. 2016).

Nonetheless it cannot be excluded that a higher magnesium sulfate dose might have resulted in more pronounced clinical effects.

Pain assessment in non-verbal patients might be extraordinarily challenging even for experienced observers, especially when subjective indicators, namely behavioural signs of pain, are evaluated (Conzemius et al. 1997; Reid et al. 2007). The choice of having one single investigator in charge for all the assessments, as well as of using several pain scales instead of one, should have overcome some potential intrinsic limitations, namely the inter-observer variability and poor sensitivity and specificity of the scale used to evaluate pain.

Another potential limitation of this study is the absence of an irrefutable proof that the needle had been correctly placed within the epidural space in all dogs. Although the hanging drop technique was used to guide needle's insertion, and radiography to verify the needles' position within the targeted intervertebral space, only epidurography, accomplished with the injection of a contrast medium, would have inarguably confirmed that the tip of the needles had reached the adequate depth. Due to ethical considerations regarding to client-owned dogs, the use of invasive or potentially harmful techniques for this purpose could not be considered. Failure in identifying the exact injection site would have distorted the results; however, the requirement of no or little post-operative rescue analgesia, together with the detection of motor block in all dogs at recovery, suggests that the epidural injections were correctly performed.

Assuming that all the injections had been performed within the epidural space, an alternative possible explanation for the lack of differences between the two treatments is that ropivacaine alone, at the dose and concentration used in the current study, might already be adequate as analgesic treatment for hip replacement. Moreover carprofen, which was given to all dogs in recovery, might also contributed to post-operative analgesia. In this scenario, detecting an appreciable difference would be more challenging and possibly require a larger sample size. Unfortunately, the use of a suboptimal analgesic treatment instead of ropivacaine would have raised some ethical concerns and was for this reason regarded as an unsuitable option.

In the dogs enrolled in the current study plasma magnesium concentrations were not measured. Although 2 mg kg^{-1} of spinal magnesium sulphate were found not to significantly increase total plasma magnesium concentrations in dogs (Adami et al. 2016), it cannot be

assumed that the same dose administered epidurally would have similar uptake and redistribution. As a consequence, mild hypermagnesaemia might have gone undetected in the dogs enrolled in the current study. However, it is reasonable to assume that a clinically relevant hypermagnesaemia would have been accompanied by cardiac arrhythmias and, possibly, persistent hypotension, none of which was not noticed in the study population.

CONCLUSIONS

In conclusion, the addition of 2 mg kg^{-1} magnesium sulphate to epidural ropivacaine did not result in considerable improvement of quality and duration of peri-operative analgesia, but neither prolonged the motor block. Further trials investigating a greater number of animals are needed to determine whether a higher dose of magnesium administered via the epidural route would increase the analgesic effect in dogs undergoing orthopaedic surgery.

ABSTRACT

Objective

The aim of this study was to determine whether lumbosacral epidural administration of magnesium sulphate added to ropivacaine prolongs and improves perioperative analgesia, without adverse effects on motor block duration or hind limb neurological function, in dogs undergoing hip arthroplasty.

Study design

Investigator-blind, controlled, randomized, prospective clinical trial.

Animals

Twenty client-owned dogs undergoing hip arthroplasty were randomly allocated to: group C (control, receiving 1 mg kg^{-1} epidural ropivacaine) or group M (magnesium, injected epidurally with a mixture of 1 mg kg^{-1} ropivacaine and 2 mg kg^{-1} magnesium sulphate).

Methods

Dogs received acepromazine, propofol and isoflurane. Intraoperatively, nociception was assessed on the basis of changes in physiological variables above baseline values. Postoperatively, pain was evaluated with a Sammarco pain score, a Glasgow pain scale and a visual analogue scale. A Tarlov scale was used to quantify motor block. All dogs were evaluated at recovery and then 1, 2, 3, 4, 5 and 24 hours after that. Rescue analgesia was provided during surgery with fentanyl and, postoperatively, with buprenorphine.

Results

The two treatment groups did not differ ($P > 0.05$) with respect to intraoperative physiological variables, rescue analgesia, postoperative pain scores (Sammarco $q = 1.00$; Glasgow $q = 3.10$; VAS $q = 0.50$) and duration of the motor block (Tarlov's $q = 2.40$).

Conclusions and clinical relevance

The addition of epidural magnesium to ropivacaine did not improve, neither did it prolong, the analgesia provided by ropivacaine alone. Further studies are needed to determine whether an epidural magnesium dose higher than 2 mg kg^{-1} would exert better analgesia, without causing adverse effects, in dogs undergoing orthopaedic surgery.

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