Aus dem Zentrum für klinische Tiermedizin

der Tierärztlichen Fakultät

der Ludwig-Maximilians-Universität München

Arbeit angefertigt unter Leitung von: Univ.-Prof. Dr. med. vet. U. Matis

Evaluation of Metamizole and Carprofen as postoperative analgesics in canine total hip replacement

Inaugural-Dissertation

zur Erlangung der tiermedizinischen Doktorwürde

der Tierärztlichen Fakultät der Ludwig-Maximilians-Universität

München

von

Andrea Stotz Rudolff

aus Antofagasta

München 2011

Gedruckt mit der Genehmigung der Tierärztlichen Fakultät

der Ludwig-Maximilians-Universität München

Dekan: Univ.-Prof. Dr. Braun

Berichterstatter: Univ.-Prof. Dr. Matis

Korreferent/en: Univ.-Prof. Dr. Ammer

Tag der Promotion: 12. Februar 2011

A mi familia

CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

AA	4-amino antipyrine	$\mu g \cdot kg^{-1} \cdot h^{-1}$	Microgram per kilogram per hour
AAA	Acetyl-amino-antipyrine	mMPS	Modified Melbourne pain scale
Aβ	A beta	NA	Noradrenaline
Aδ	A delta	NK	Neurokinin
AMPA	α-amino-3-hydroxy 5-methyl-4-isoxazelopropionic acid	NMDA	*N*-methyl *D*-aspartate
C	Carprofen	NO	Nitric oxide
cGMP	Cyclic guanosine monophosphate	NOS	Nitric oxide synthase
cNOS	Constitutive nitric oxide synthase	Nop	Non operated limb
COX	Cyclooxgenase	NRS	Numerical rating scale
CRI	Constant rate infusion	NSAID	Non steroidal anti-inflammatory drug
DRG	Dorsal root ganglion	NS	Nociceptive specific neurons
DRN	Dorsal raphe nucleus	Ns	Newton per second
FAA	4-formyl-amino-antipyrine	O_2	Oxygen
Fig	Figure	Op	Operated limb
GABA	Gamma amino-butyric acid	OP1	First postoperative day
GI	Gastrointestinal	OP2	Second postoperative day
GRF	Ground reaction force	PAG	Periaqueductal gray matter
IASP	International association for the study of pain	PB	Parabrachial area
IL	Interleukine	PG	Prostaglandins
iNOS	Inducible nitric oxide synthase	PGD_2	Prostaglandins D_2
IV	Intravenously	PGE_2	Prostaglandins E_2
kgBW	Kilogram body weight	preOP	Preoperative day
LC	Locus coerelus	PVI	Peak vertical impulse
L-NAME	L-Nitro-arginine methyl ester	SNP	Sodium nitroprusside
L-NMMA	L-NG-monomethyl arginine	STT	Spinothalamic tract
L-NOARG	L-NG-nitro arginine	THR	Total hip replacement
M	Metamizole	TX	Tromboxane
MAA	4-methyl-amino-antipyrine	VAS	Visual analogue scale
$mg \cdot kg^{-1}$	Milligram per kilogram	WDR	Wide dynamic range neurons
$\mu g \cdot kg^{-1}$	Microgram per kilogram	5-HT	5-Hydroxytryptamin (serotonin)

I. INTRODUCTION

Description and, more exactly, the recognition and subsequent proper evaluation of pain are very difficult. Pain is a universal and subjective unpleasant experience commonly associated with tissue-damaging stimuli. It is a sensitive stimulation of individual origin which is difficult to evaluate in animals, because of the lack of objective systems to recognize this experience (AIGÉ AND CRUZ, 2001; WATERMAN-PEARSON, 2001). People can verbally express their feelings whereas the evaluation of nociception in animals requires dedication and understanding of the different behavioural and physiological changes that an animal will present. The observation of evident signs and their correct interpretation are necessary to recognize the experience of pain (HELLEBRECKERS 2002, STASIAK et al. 2003). In the past animals were considered to have an inferior level of development than human beings and consequently it was believed that they could not feel pain in the same way as humans. Nonetheless it has been observed that animals respond with violent movements, vocalisations and aversive behaviours when hurt (HELLEBRECKERS 2002, WATERMAN-PEARSON 2001).

The ability to feel pain has an advantage in survival because it limits the extension of the injury, provokes rest and wound healing, assuring that the animal learns to avoid noxious stimuli. In other terms it is an alarm sign essential to survival or a protective reflex, whose purpose is withdrawal of the damaged tissue away from potentially noxious stimuli. However, continuous pain sensation induces stress that, when severe, may threaten the animal's well-being (CAILLIET 1995, WATERMAN-PEARSON 2001). Many veterinary practitioners do not feel the necessity to treat their patients for pain, because they conclude that an animal walking and eating normally cannot be suffering from pain and therefore does not need analgesics (GAYNOR 1999).

The lack of attention to pain therapy is mainly due to a tendency to misinterpret the external signs of pain as well as due to a lack of appreciation for the importance of it (GARCÍA and YNARAJA 1999). Today it is recognized that control and treatment of pain is an essential part of a professional and conscientious handling of animals (AIGÉ AND CRUZ 2001).

II. LITERATURE

1. Physiology of pain

1.1. Definition of pain

It is prudent to differentiate the term pain from nociception. The International Association for the Study of Pain (IASP) defines pain as 'a sensorial or unpleasant emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (HELLEBRECKERS, 2002; HELLYER 2007). This definition incorporates a psychological component, which can alter pain perception (MELLO and DICKENSON, 2008). The sensation of pain is well known in humans, because it can be verbally defined. Animals, conversely, cannot verbally express their feelings making it impossible to know if they feel pain as described by humans (DEGENAAR, 1979). However, the inability to communicate does not negate the possibility that an individual is experiencing pain and, moreover, noxious stimuli in animals elicit reflex withdrawal, behavioural, neuroendocrine and autonomic nervous system responses comparable to humans (MUIR and WOOLF, 2001). The term nociception is related to the recognition of the noxious stimulus in the central nervous system that originates in sensitive receptors providing the information related to the damaged tissue (HELLEBRECKERS, 2002; LEMKE, 2004).

1.2. Nociception

Nociception can be defined as the transduction, transmission, modulation and central nervous system processing of the signals produced upon stimulation of specific receptors. It is the physiological process that, once finished, produces the conscious perception of pain (TRANQUILLI et al., 2001; LEMKE, 2004). Transmission occurs through a three-neuron chain (fig. 1). A noxious stimulus in the periphery activates a primary afferent fibre 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 tertiaty neuron transmits the modified noxious stimulus to higher brain centers, notably the cerebral cortex, for perception (LEMKE, 2004).

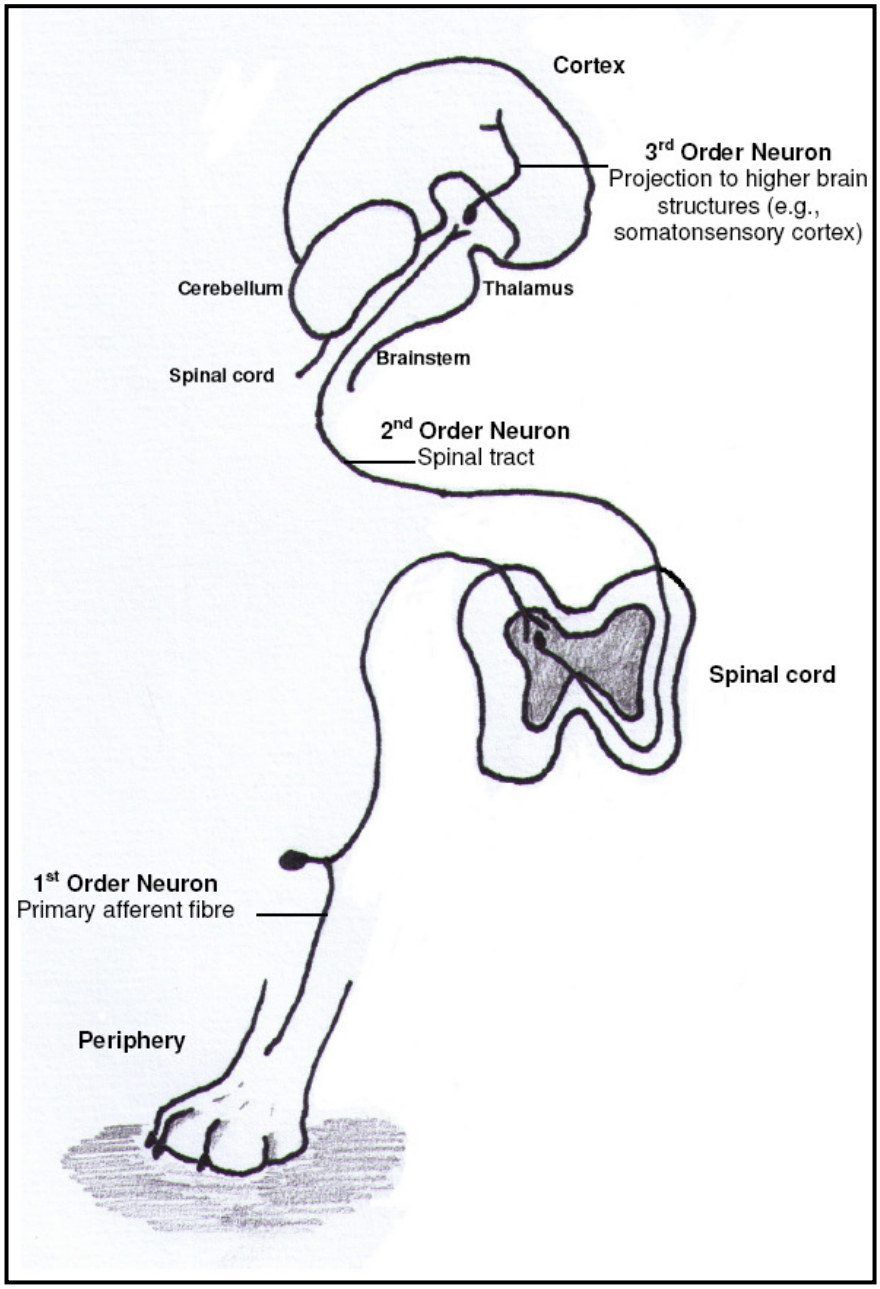

Figure 1: A simplified representation of nociceptive processing as a three-neuron chain (LEMKE et al. 2004).

1.2.1. Peripheral receptors

The transduction is the appreciation of different types of inciting stimuli. It is the encoding through peripheral receptors of familiar sensations such as temperature, touch and pain (mechanical, chemical, or thermal energy) into electric impulses. These receptors in the skin can be further classified according to sensory modality. For example, thermoreceptors respond to warming or cooling of the

skin, whereas mechanoreceptors respond to pressure, stretch or hair movement. In addition to these neurons that respond to innocuous touch and temperature, sensory neurons known as nociceptors initiate painful sensations. Many nociceptors are polymodal neurons that are activated by various types of sensory stimuli (LAMONT et al., 2000, LUMPKIN and CATERINA, 2007). Polymodal receptors respond to both mechanical and thermal or chemical stimuli. Chemical stimuli are substances liberated in damaged tissues like bradykinin (main cause of pain), serotonin, histamine, potassium ions, acids (lactic acid in case of ischemia), acetylcholine, proteolytic enzymes and prostaglandins (PGs) (LEMKE, 2004). The sensitivity of nociceptors to sensory stimulation can be altered by signalling pathways engaged during injury or inflammation (LUMPKIN and CATERINA, 2007).

1.2.2. Afferent nerve fibres

Following the transduction, the transmission of the pain stimulus takes place. The impulse is projected along the first-order neuron from the periphery to the dorsal horn of the spinal cord. Nociceptors are present in the nerve endings of about 70% of all peripheral nerve fibres (TORREGROSA, 1994; CAILLIET, 1995; LAMONT et al., 2000). In the case of mechanical and thermal receptors the first-order neurons correspond to myelinated afferent Aδ fibres of small diameter that carry high-speed stimuli (5-30 m/s). These Aδ fibres are responsible for the “first acute pain”, which is often described as a sharp, stinging, or pricking sensation (fig.2). Aδ fibres are activated, for example, during the withdrawal reflex. In this case a precise localization of the pain perception is possible. In contrast, if the stimulus is of sufficient magnitude, mechanoheat or polymodal receptors reinforce the response of the Aδ fibres through the activation of non-myelinated type C fibres of small diameter and low-speed nerve conduction velocity (0,5 – 2 m/s). These fibres are responsible for the “second” or “slow pain”, which is frequently diffuse, constant and persistent. Both Aδ and C fibres are located throughout the skin, peritoneum, pleura, periosteum, subchondral bone, joint capsules, blood vessels, muscles, tendons, fascia, and viscera, although their distribution density varies depending on the species and anatomic location (LAMONT et al., 2000; MUIR and WOOLF, 2001). In the visceral tissue type C fibres respond to situations like ischemia, irritation and tension. They do not only transmit pain but also release vasodilator substances, generate neurogenic oedema and sensitize the

nerve terminals (GARCÍA and YNARAJA, 2001; LEMKE, 2004). Another type of afferent fibres are the large diameter and highly myelinated Aβ fibres, which quickly conduct action potentials from the periphery to central terminals. These fibres have low activation thresholds and normally respond to light touch. They are mainly responsible for conveying tactile non painful information (MELLO and DICKENSON, 2008).

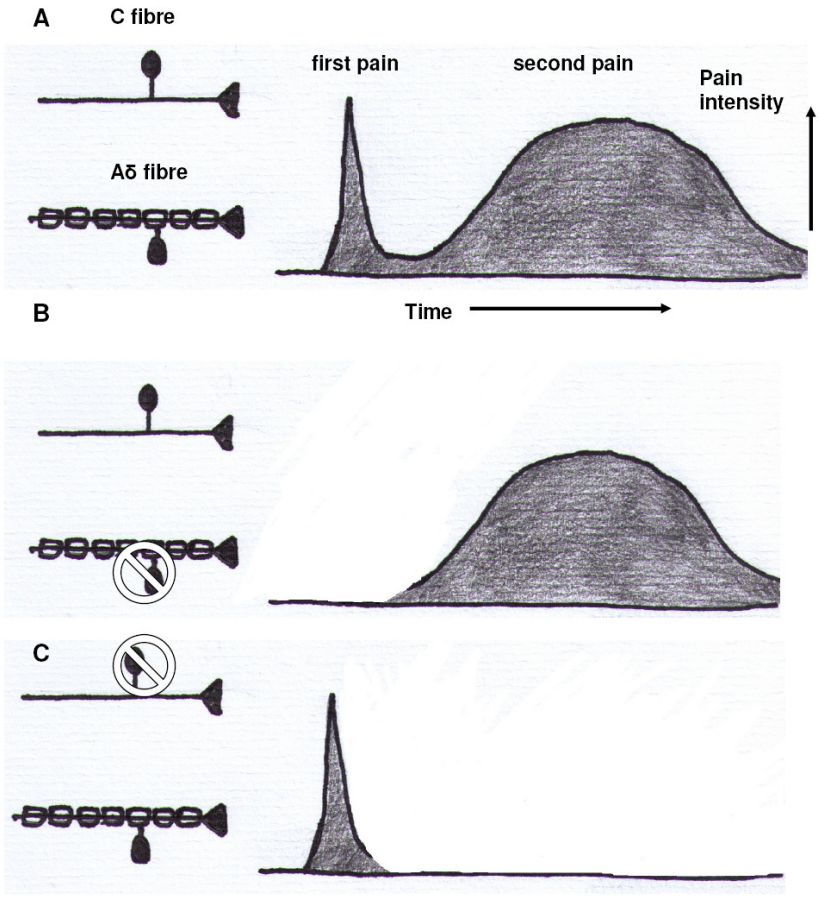

Figure 2: Primary afferent pain transmission. First pain and second pain sensations after a noxious stimulus (A). The first pain sensation is abolished when the A fibres are blocked (B), while the second pain sensation is abolished when the C fibres are blocked (C) (LAMONT et al., 2000).

1.2.3. Dorsal horn neurons

All afferent nerve fibres enter the spinal cord through the dorsal root, where the processing and modulation of the signals takes place. Cell bodies of both types of afferent nerve fibres (Aδ and C) are located in the dorsal root ganglia and extend axons to synapse with second-order nociceptive neurons in the dorsal horn of the

spinal cord. On the spinal level there are three main types of nociceptive neurons: interneurons, propriospinal neurons and projecting neurons, all of which are organized in different laminae or layers. Neurons responsible for nociceptive mediation are located primarily in lamina I (marginal layer), lamina II (substantia gelatinosa), and lamina V. The majority of the Aδ fibres terminate in the most superficial layer with some fibres projecting more deeply to lamina V. Most C fibres send their axons to the superficial dorsal horn, with the focus in lamina II but also send a few branches to laminae I and V (LAMONT et al., 2000; MUIR AND WOOLF, 2001), whereas myelinated Aβ fibres innervate deeper laminae III-VI (MILLAN, 2002; MELLO and DICKENSON, 2008) (fig. 3). The deepest dorsal horn neurons also receive direct or indirect inputs from A-fibre nociceptors (HEINRICHER et al., 2009).

The interneurons frequently are divided into excitatory (glutamatergic) and inhibitory ($GABA_{ergic}$) subtypes (MELLLO and DICKENSON, 2008), which serve as relays and participate in local processing. Propriospinal neurons extend over various spinal segments and are involved in segmental reflex activity and interactions among stimuli acting at separate places. Projection neurons are located in lamina I and V and participate in rostral transmission by extending axons beyond the spinal cord to supraspinal third-order neurons ending in supraspinal centres such as the midbrain and the cortex (LAMONT et al., 2000; LEMKE, 2004).

Projection neurons have been also subclassified into two groups: (1) Nociceptive specific (NS) neurons are concentrated in lamina I and are excited solely by noxious mechanical or thermal input from both Aδ and C fibres. They are somatotopically arranged and respond to afferent impulses originating from discrete topographic areas. (2) Wide dynamic range neurons (WDR) predominate in lamina V and receive innocuous input from low-threshold mechanoreceptors (Aβ fibres) as well as nociceptive information (fig. 3). They respond in a graded manner over a larger receptive field than do NS neurons and often receive convergent deep and visceral input (LAMONT et al., 2000; MILLAN, 2002, MELLO AND DICKENSON, 2008). They constitute a strategic site where various types of excitatory and inhibitory influences converge (LE BARS, 2002).

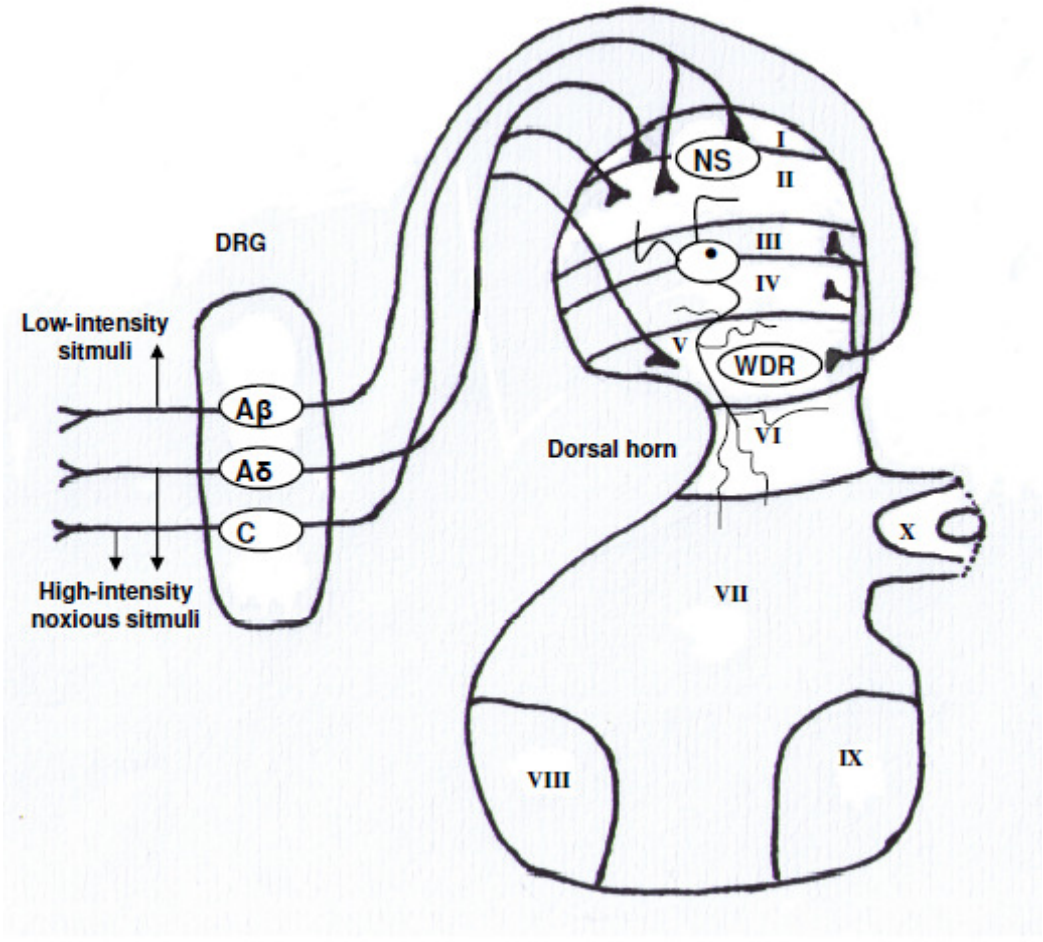

Figure 3: Pain pathways from the periphery to the brain. Primary afferent fibres (Aβ-, Aδ-, and C-fibres) transmit impulses from the periphery, through the dorsal root ganglion (DRG) and into the dorsal horn of the spinal cord. Nociceptive specific (NS) cells are mainly found in the superficial dorsal horn (lamina I-II), whereas most wide dynamic range (WDR) neurons are located deeper in lamina V (MELLO and DICKENSON, 2008).

The communication of nociceptive information occurs via chemical signalling mediated by excitatory and inhibitory amino acids and neuropeptides. Nociceptive Aδ and C fibres, as well as non-nociceptive fibres, co-release excitatory amino acids (glutamate and aspartate) and neuropeptides (substance P, neurokinin A, calcitonin gene-related peptide (CGRP) and cholecystokinin) that bind to distinct receptors on dorsal horn neurons, among which the α-amino-3-hydroxy 5-methyl-4-isoxazelopropionic acid (AMPA) receptor and the *N*-methyl-D-aspartate (NMDA) receptor are of great significance (MUIR and WOOLF, 2001; MELLO

and DICKENSON, 2008). MILLAN (2002) also mentions the activation of tachykinin (NK) 1- (preferred ligand: substance P) and possibly NK2- (preferred ligand: neurokinin A) and NK3-receptors (preferred ligand: neurokinin B), which play an important role in nociceptive transmission. NK1 receptors are mostly distributed in lamina I (MORRIS et al., 2004).

1.2.4. Ascending spinal tracts

All nociceptive inputs are conveyed to supraspinal centres by projection neurons. A large population of these projection neurons is found superficially in laminae I and it is estimated that 80% of these cells express NK1 receptor for substance P. NK1-positive fibres project to areas in the brain such as the thalamus, the periaqueductal grey (PAG), and the parabrachial area (PB) (TODD, 2002). These projections are achieved through one of several pathways: the spinothalamic tract (STT) is one of the more important and prominent nociceptive pathways. It originates from the axons of NS and WDR neurons in laminae I, V, VI and VII which cross the midline and project to the thalamic nuclei and then via third order neurons to the limbic system and to the somatosensory cortex; it is responsible for the affective and emotional component involved in pain transmission and the sensory- discriminative aspects of pain sensation.

Axons located more deeply in laminae VII and VIII form the spinoreticular tract that projects to the reticular formation in the medulla and pons, to thalamic nuclei and then to the somatosensory cortex. The reticular formation is crucial for the integration of nociceptive input. Ascending reticular activity increases cortical activity, while descending reticular activity blocks other sensory activity.

Finally nociceptive neurons originating in laminae I and V project in the spinomesencephalic tract to the mesencephalic reticular formation, the lateral part of the periaqueductal gray matter (PAG), and several other midbrain sites. The PAG plays a central role in the integration and modulation of nociceptive input at the supraspinal levels (LAMONT et al., 2000; MUIR and WOOLF, 2001; LEMKE, 2004).

2. Pathophysiology of pain

2.1. Causes of pain

Independent of the quality (chemical, thermal or mechanical) of a noxious stimulus the peripheral nervous system transforms the stimulus energy into electrical energy for its subsequent recognition in the CNS (TRANQUILLI et al., 2001). The visceral tissue, unlike the skin, is not highly sensitive to stimuli like pricking or the incision of a scalpel and normally this is not associated with intense pain, but it does respond to damaging processes like ischemia, spasm and overdistension (STOELTING AND HILLIER, 2006). Nociceptors present different activating thresholds depending basically on their localization (somatic or visceral). Upon tissue damage (cell destruction), potassium and several inflammatory mediators are released, including but not limited to PG, bradykinin, leukotriens, 5-hydroxytryptamine (5-HT), histamine, substance P, thromboxane, and platelet-activating factor. All of these neuroactive substances constitute a sensitizing soup that synergistically works to sensitize high-threshold nociceptors to mechanical, thermal, or chemical stimuli. The transmission of stimuli in the spinal cord is determined by, among others, the activation of spinal receptors which respond to substance P, glutamate or PG (WOOLF and CHONG, 1993; GARCÍA and YNARAJA, 1999; MUIR and WOOLF, 2001; VANEGAS and SCHAIBLE, 2001; LEMKE, 2004). PG released in the spinal cord enhances the production of glutamate and aspartate, both mediators then act pro-nociceptive at supraspinal levels (VANEGAS and SCHAIBLE, 2001; HEINRICHER et al., 2004). On the other side, at supraspinal levels cyclooxygenase isoforms are tonically active in the PAG, too, and their products exert a facilitatory effect on acute spinal nociceptive processing, which preferentially targets C-nociceptors in the dorsal horn (LEITH et al. 2007). Involvement of nitric oxide (NO) in the mediation of pain has also been studied. The intracutaneous injection of NO evokes pain in humans (HOLTHUSEN and ARNDT, 1994). Nitric oxide may also contribute to the transmission of excitatory impulses between primary afferents and secondary dorsal horn neurons (BUDAI et al., 1995). However, a pronociceptive activity of NO is controversial, since the antinociception produced by several analgesics is mediated through NO synthesis via the L-arginine-NO-cGMP pathway (DUARTE et al., 1992; IWAMOTO and MARION, 1994; SONG et al., 1998; SACHS et al., 2003).

The incision of tissue produces injury and cell destruction, hence the liberation of several inflammatory mediators. These mediators are the main reason why a surgical process is potentially painful (MUIR and WOOLF, 2001). TRANQUILLI (1997) classified different surgical processes according to their ability to produce pain. This classification lists moderately painful mainly soft tissue surgical interventions, e.g. ovariohysterectomy, castration, and laparotomy, and severely painful interventions, e.g. thoracotomy or osteosynthesis.

Although alloarthroplasty of the hip (total hip replacement) in dogs with coxarthrosis ensures a fast pain alleviation and total limb function after surgery (MATIS, 1995), the procedure includes soft tissue damage as well as bone dissection and therefore can be scored as a severely painful intervention, both intraoperatively and in the postoperative period (SCHEBITZ and BRASS, 1999).

2.2. Types of pain

According to the anatomical disposition of the nociceptive fibres and to their physiology, pain can be classified in two ways: somatic pain and visceral pain. Somatic tissues have more nociceptors and smaller receptive fields, while visceral tissues have fewer nociceptors and larger receptive fields (LAMONT et al., 2000). These anatomic differences may account for some of the qualitative differences between somatic (discrete) and visceral (diffuse) pain. Somatic pain can also be divided into superficial and deep pain. The superficial pain becomes evident when stimulating mechano- and heat receptors and is transmitted through Aδ fibres. Deep pain, conversely, is associated with the liberation of chemical substances which stimulate the nerve endings of type C fibres (TRANQUILLI et al., 2001, WATERMAN-PEARSON, 2001). Visceral pain is characterized by its difficulty to be localized and often it is referred to somatic areas. Here the sensations are carried through two different pathways: by a true visceral pathway or/and a parietal pathway. The parietal pathway is more specific, picks up sensations from body cavity walls and is formed by somatic fibres that are part of the spinal nerves. The visceral pathway on the other hand is not well defined; it follows the sympathetic and parasympathetic fibres, and transmits the information from organs located in the abdominal, thoracic and pelvic cavity (AIGÉ and CRUZ, 2001). Parenchyma of the brain, liver and alveoli of the lungs are devoid of pain receptors. Nevertheless, the bronchi and parietal pleura are very sensitive to pain (STOELTING and HILLIER, 2006). Visceral nociceptor stimulation usually

produces pain that is poorly localized. However, within the spinal cord, the ascending pathway for visceral nociception coincides at least in part with that for somatic nociception (GRIMM and WAGNER, 2007).

2.3. Sensitization (Wind up)

Sensitization is the result of neural plasticity. Plasticity is defined as the capacity of the nervous system to modify its function in response to different environmental stimuli. These changes occur in the periphery (peripheral sensitization) and in the CNS (central sensitization) (CODERRE et al., 1993).

In a clinical setting, even relatively innocuous wounds are associated with a degree of tissue inflammation able to initiate a cascade of sensitizing cellular events. Damaged cells and primary afferent fibres release a number of chemical mediators, which promote vasodilation with extravasation of plasma proteins and recruitment of inflammatory cells. The peripheral sensitization depends on vasoactive amines liberated from damaged tissue and inflammatory cells, and on the liberation of neuropeptides from nociceptive nerve endings (type C fibre). An inflammatory soup is created, composed of several vasoactive amines, ions and different subproducts of the arachidonic acid, that create a sensitizing environment (MUIR and WOOLF, 2001). This effect causes the originally high threshold nociceptors to respond to stimuli of low intensity (sleeping receptors). Sleeping or silent nociceptors are activated by inflammatory mediators and respond to mechanical and thermal stimulation only after they have been activated. The activation of these nociceptors contributes to the peripheral sensitization and the primary hyperalgesia (HARDY et al., 1950; RAJA et al., 1984). In addition to primary hyperalgesia associated with damaged tissue, pathological pain can also invoke an increased sensibility of neighbouring areas to noxious (secondary hyperalgesia) as well as to innocuous mechanical stimuli (allodynia) (HARDY et al., 1950; TOREBJÖRK et al., 1992; CODERRE et al., 1993). These clinical hypersensitivities (secondary hyperalgesia and allodynia) are a result of dynamic changes in dorsal horn neuron excitability, which modifies their receptive field properties. These stages are related to the duration of the synaptic action potentials generated by Aδ and C fibres. An action potential may last up to 20 seconds, resulting in a summation of potentials and creating a progressively increasing and long-lasting depolarization in dorsal horn neurons (WOOLF, 1983). This so-called “windup” of spinal neurons is mediated by NMDA

receptors, which bind glutamate, and tachykinin receptors (WOOLF and THOMPSON, 1991; MELLO and DICKENSON, 2008). Other types of afferent neurons (large, myelinated Aβ fibres) respond to non-noxious stimuli (touch) but not to noxious stimuli directly. During central sensitization these fibres are recruited. Once the dorsal horn has been sensitized by nociceptive input, activation of Aβ fibre mechanoreceptors by previously innocuous tactile stimuli actually contributes to the pain response. In the dorsal horn, WDR neurons exhibit great activity and are largely involved in the encoding process of central sensitization whereas NS neurons do not participate intensively (MAIXNER et al., 1986). The WDR neurons respond normally to innocuous stimuli but, once they are sensitized, they react to any stimulus and produce chronic central pain (DUBNER, 1990; ZHANG et al., 2005).

In conclusion, the increase in spinal excitability is also accompanied by an increase in the receptive field, and in the duration and intensity of the stimulus response, leading to a hypersensible and hyperactive state at spinal levels. Both phenomena, the central and peripheral sensitization, are the fundamental basis for an analgesic approach that implies the preemptive administration of analgesic drugs before a noxious stimulus can trigger a sensitizing reaction (WOOLF and CHONG, 1993; LASCELLES et al., 1994; LASCELLES et al., 1997; HEYLLER, 1999, SHAFFORD et al., 2001; TRANQUILLI et al. 2001; WATERMAN-PEARSON, 2001; JIN and CHUNG, 2001; HELLEBRECKERS, 2002; GONZALEZ de MEJÍA, 2005).

3. Pain as a pathology

An important conceptual breakthrough in understanding pain physiology was the recognition that the pain occurring after most types of noxious stimulation is usually protective and quite distinct from the pain resulting from deliberate damage to tissues or nerves. This first type of pain is termed “physiologic pain”, and plays an integral adaptive role as part of the body’s normal defence mechanisms, warning of contact with potentially damaging environmental insults and initiating behavioural and reflex avoidance strategies (LAMONT et al., 2000). This type of pain requires noxious (high threshold) input, is discrete (well-localized) and transient. Pathological pain, on the other hand, is defined as the type of pain that animals experience following severe trauma (e.g. surgery). It

subsequently requires non-noxious stimuli (low threshold), and it is diffuse and prolonged in duration. This type of pain does not serve a protective action (LEMKE, 2004). Pathologic pain is a physical and emotional experience that exceeds every beneficial effect (SHAFFORD et al., 2001; HELLEBRECKERS, 2002). It provokes respiratory distress and increases the activity of the sympathetic nervous system which eventually causes metabolic and physiological dysfunctions like increasing serum concentrations of catecholamines, glucose and cortisol. Furthermore, the serum elevation of ACTH leads to the release of the antidiuretic hormone, aldosterone, renin and angiotensin II. All of these factors produce peripheral vasoconstriction, hence predispose to myocardial alterations and arrhythmias. Tachypnoea and dyspnoea decrease the partial pressure of oxygen and also promote the formation of atelectases and development of pneumonias (GAYNOR, 1999; GRECO and STABENFELDT, 2003; HELLYER, 2007). Besides, the perception of pain causes an altered metabolic state and emotional suffering. It provokes anxiety and may provoke sleep deprivation leading to physic and psychic alterations which seriously complicate any healing process (wound dehiscence) (WOLFF and CHONG, 1993; LAUTENBACHER et al., 2006).

4. Pain management

4.1. Descending control of pain

The CNS has its modulation system - a pain control mechanism in the spinal cord and in the brainstem (MILLAN, 2002). These descending pathways from brainstem and cortical structures have both facilitatory and inhibitory effects on nociceptive signalling in the dorsal horn and thalamus (HEINRICHER et al., 2009). An increased inhibitory drive is presumably a homeostatic mechanism initiated in an attempt to counteract an enhanced facilitatory drive and increased spinal hyperexcitability (MELLO and DICKENSON, 2008). Thus, one can conceive that pathological processes may disrupt the equilibrium between excitatory and inhibitory influences, notably when inhibitory controls are lacking (LE BARS, 2002).

The periaqueductal grey matter (PAG), rostral ventromedial medulla (RVM), the nucleus raphe magnus (NRM) and the locus coeruleus (LC) are all key brainstem sites for the modulation of nociceptive transmission in the spinal cord

(STAMFORD, 1995; HEINRICHER et al., 2009). The PAG projects to the RVM, which in turn sends its output mainly, although not exclusively to the superficial dorsal horn laminae, an important place for nociceptive processing and modulation. Recently, studies proved that descending control from the PAG differentially inhibits C- vs. A-fibre-evoked events in deep dorsal horn laminae but inhibits both C- and A-fibre-evoked events in lamina I (KOUTSILOU et al., 2007).

Descending modulation is exerted by three main neurochemical systems – the noradrenergic, serotonergic and opioidergic systems (TAVARES and LIMA, 2007). Some neuromodulators that participate in this process are serotonin (5-HT), endorphin and encephalin. More recently noradrenaline (NA) has been shown to have an equally important role in the control of pain. In this respect the alpha$_2$-receptor subtype is responsible for the mediation of the antinociceptive effect (STAMFORD, 1995; MELLO and DICKENSON, 2008). The existence of several neurotransmitters and multiple receptors differentially modifies neuronal activity, corresponding to a bi-directional facilitatory and/or suppressive influence of certain mediators (MILLAN, 2002). The RVM, for example, is kwon for its biphasic effect (TODD, 2002). The NRM within the RVM forms a component of a descending inhibitory network that modulates nociceptive neurotransmission at the level of the spinal cord dorsal horn (MARINELLI et al., 2002). These can farther be influenced by the recruitment of RVM ON-cells and OFF-cells. When the ON-cells population is active, pain facilitation predominates, whilst an increase in OFF-cells population suppress pronociception (HEINRICHER et al., 2009).

Opioids are involved in both ascending and descending components of pain modulation. In the ascending part, all three receptors (μ, δ, κ) play an important role. The PAG is rich in opioid receptors and endogenous opioids and is a major target of analgesic action in the central nervous system. Moreover, moderate μ-receptor binding is found in the dorsal raphe nucleus (DRN) and NRM with higher density in LC. It has been proposed that the analgesic effect of opioids on the PAG works by suppressing the inhibitory influence of the neurotransmitter γ-aminobutyric acid (GABA) on neurons that form part of a descending antinociceptive pathway (STAMFORD, 1995; VAUGHAN et al., 1997). The PAG and NRM are under GABA$_{ergic}$ inhibitory control and the microinjection of

$GABA_a$ receptor agonist into PAG causes hyperalgesia and also blocks the antinociceptive action of locally applied morphine (STAMFORD, 1995).

4.2. Pain management

Apart from the use of local anaesthetics total pain relief cannot be achieved by a single drug or method. Therefore combined anaesthetic regimens are more and more recommended. The rationale behind this strategy is to obtain profound analgesia due to additive or synergistic effects of different analgesics agents. This method is known as “balanced” or “multimodal analgesia”, and the goal is to achieve sufficient analgesia with concomitant reduction of side effects due to resulting lower drug doses (KEHLET and DAHL, 1993; STAMFORD, 1995; JIN and CHUNG, 2001). The reduced demand for analgesics with preservation of pain relief may be important in reducing side effects and thereby the need for postoperative surveillance. The concept of balanced analgesia may have an important impact on postoperative convalescence and morbidity (DAHL et al., 1990). A study by LASCELLES et al. (1995) demonstrated a benefit by pre-emptively using an analgesic drug at a clinically relevant dose rate. In order to prevent the onset of hypersensitivity probably the best approach is to administer analgesics both pre-, intra- and postoperatively (WOLF and CHONG, 1993).

Analgesic drugs can act on different parts of the nociceptive pathway depending on their pharmacological properties. It is possible to combine different drugs and techniques to partially inhibit the release of inflammatory mediators and to decrease the conductance of the nociceptive information to superior levels (KEHLET and DAHL, 1993). At present, several analgesic techniques or a combination of these techniques are available to use: at the peripheral level local anaesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, opioids, and α_2-agonists reduce or inhibit the transduction/ transmission of nociceptive information; at the spinal cord level the use of local anaesthetics, opioids, α_2-agonists and NMDA-receptor antagonists may serve to inhibit central sensitization. At the cortical level the use of opioids, α_2-agonists and hypnotic anaesthetics inhibits the perception of pain (fig. 4) (KEHLET and DAHL, 1993).

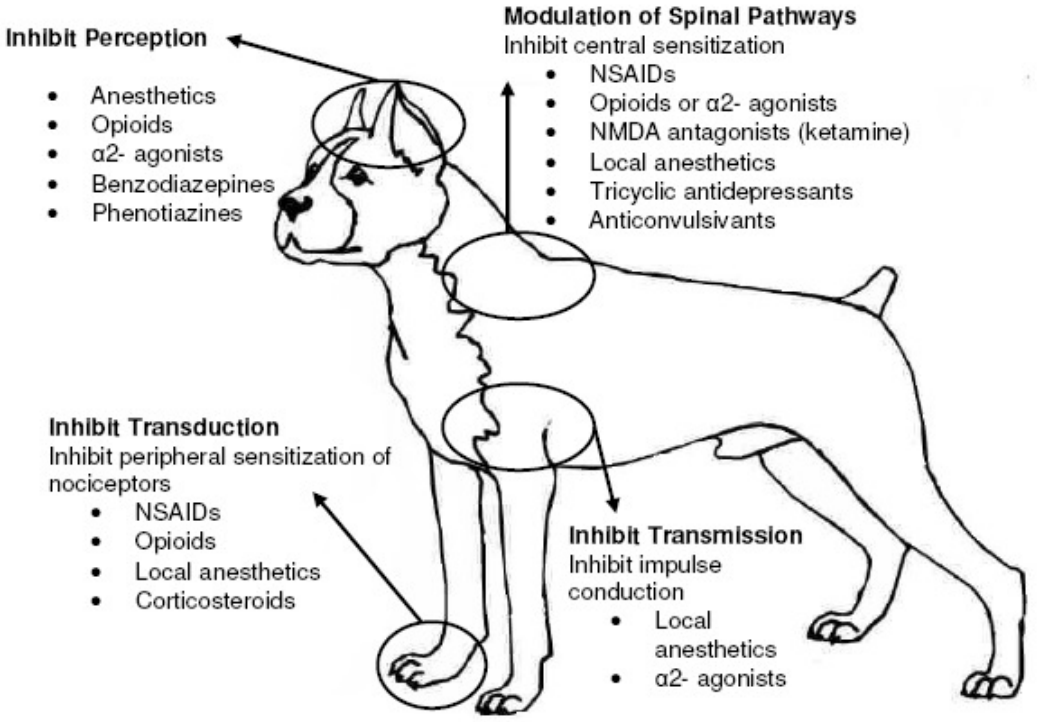

Figure 4: The site of action of the major classes of analgesics as they affect transduction, transmission, and modulation of nociceptive input and the perception of pain (TRANQUILLI et al., 2001).

4.2.1. Opioids

Opioids are the most effective analgesics, especially for moderate-to-severe postoperative pain. The discovery of the opioid receptor followed by the isolation and identification of the endogenous opioid peptides has had impact on the treatment of pain. The endogenous opioids, the enkephalins, dynorphins and endorphin family are all peptide in nature. Systemic opioids act both presynaptically to reduce neurotransmitter release and postsynaptically to hyperpolarize the membrane of dorsal horn neurons (DICKENSON, 1991; JIN and CHUNG, 2001). All of them have a similar mechanism of action, although the potency of the diverse receptor types is heterogeneous (μ-receptors, δ-receptors and κ-receptors) (LORD et al., 1977). The nociceptive fibres also play an important role: in an experimental study electrical stimulation of the NRM led to inhibition of nociceptive information transmission mediated by the release of endogenous opioids. Opioids preferentially attenuated C-fibre activity (both pre- and postsynaptically) through μ- and δ- opioid receptors. Aδ fibres were

modulated only postsynaptically (JONES et al., 2003; LU et al., 2004).

Some authors confirm the participation of spinal NO in the antinociceptive activity of systemically administered opioids (SONG et al., 1998). A peripheral action is described, too, suggesting that opioids may specifically reverse the hyperalgesic effect of PGE_2 and that NO formation through the L-arginine/ nitric oxide/ cGMP pathway may mediate this peripheral action (MAEGAWA and TONUSSI, 2003). After prolonged treatment a hyperalgesic effect of opioids has also been described. This opioid-induced increased pain sensitivity may be related to an inhibition of endogenous opioid release (HOOD et al., 2003; KOPPERT et al., 2003). However, several studies explain this delayed enhanced pain sensitivity through the capacity of opioids to increase the effect of glutamate at the NMDA-receptor level. NMDA-antagonists like ketamine may have a beneficial effect on this pro-nociceptive effect and may potentially counteract the development of chronic pain processes (CÉLÈRIER et al. 2000; SIMONNET and RIVAT, 2003).

Opioids posses several side effects, including nausea/vomiting, sedation, ileus, constipation, respiratory depression, and euphoria. All of them should be considered when using large doses of these drugs (DICKENSON, 1991; JIN and CHUNG, 2001). Opioids can be used for moderate or severe pain. Premedication with opioids may reduce the total dose of postoperative analgesia and can prevent central sensitization (WOLFF and CHONG, 1993; LASCELLES et al., 1995). Alternative analgesic drugs that potentiate the effect of opioids and contribute to a multimodal analgesia protocol include local anaesthetics, sedative drugs like α_2-agonists, NMDA receptor antagonists (ketamine) or anti-inflammatory drugs like NSAIDs or corticosteroids.

4.2.2. Nonsteroidal anti-inflammatory drugs (NSAIDs)

The value of NSAIDs in minor, moderate or severe pain is well documented, and although this class of drugs represents an important component of the multimodal approach to postoperative pain treatment their analgesic efficacy is too small to be used as a sole analgesic in more severe pain states,.

4.2.2.1. Mechanism of action

4.2.2.1.1. Cyclooxygenase enzyme and prostaglandin synthesis

Nonsteroidal anti-inflammatory drugs act by inhibiting the production of

prostaglandins (PGs) in the periphery and in the CNS (KEHLET and DAHL, 1993). Prostaglandins are pharmacologically potent lipids widely distributed in mammalian tissues and body fluids. They belong to a group of compounds known as eicosanoids, a product of the polyunsaturated fatty acids (arachidonic acid) of plasmalemmal phospholipids. Prostaglandins act locally in the tissues where they are produced, and since they are rapidly inactivated, may be considered as "local hormones" (VANEGAS and SCHAIBLE, 2001). The role of PGE_2 in inflammation has been elucidated and its pro-inflammatory potency is comparable with that of histamine, bradykinin, and serotonin. Indeed PGs have been reported to have leukotactic properties (PAULUS and WHITEHOUSE, 1973), and after injury, PGs - like other products of the arachidonic acid (AA) metabolism - promote pain and hyperalgesia associated with inflammation. The potentiation of bradykinin effects by PGs may stimulate synthesis and release of prostaglandins by activation of phospholipase A (VANEGAS and SCHAIBLE, 2001). Furthermore, PGs have an important effect on gastric and renal physiology, and possess a haemostatic function. They may inhibit gastric acid secretion, stimulate the production of mucus, and maintain renal blood flow (DAHL et al., 1991).

Prostaglandins are synthesized by one of two enzymes: Cyclooxygenase 1 (COX-1) or Cyclooxygenase 2 (COX-2). These two distinct isoforms of COX have been characterized. COX-1 is constitutively expressed and is involved in maintaining homeostatic functions, including the maintenance of gastric and renal integrity. In contrast the expression of COX-2 in neutrophils, macrophages, endothelial cells and fibroblasts is induced by growth factors, bacterial lipopolysaccharides, mitogens, and other proinflammatory stimuli (MARNETT, 2000). However, COX-2 is also constitutively expressed in the brain and spinal cord and it is present in neurons of all laminae, particularly laminae I-II but also in laminae III-VI and X (VANEGAS and SCHAIBLE, 2001). More recently, a brain-specific splice variant of COX-1 has been identified in dogs, termed COX-3. This enzyme is a product of the COX-1 gene, but it is biologically different from COX-1 and seems to be less active in the synthesis of PGs (CHANDRASEKHARAN et al., 2002; TERRENCE, 2006).

NSAIDs are usually defined as those agents that inhibit one or more reactions involved in the production of PG and thromboxanes (TX). The principal action of these drugs is the more or less selective blockade of COX-1 and COX-2 activity,

the first in a series of enzymes responsible for the conversion of AA to PG (fig. 4) (CARON, 2000). A secondary effect of COX-inhibitors has been proposed: COX-inhibitors may make more arachidonic acid available for the synthesis of other compounds through the action of lipoxygenases. It has been shown that these lipoxygenase products lead to a decrease in $GABA_{ergic}$ inhibition and thus an increase in postsynaptic neuron activity. In the PAG, this may lead to an enhanced descending nociceptive inhibition and thus antinociception at spinal levels (VANEGAS and SCHAIBLE, 2001).

The efficacy of NSAIDs in absence of inflammation suggests that these agents might relief pain through a central mechanism. Data has confirmed their effect both on the spinal cord as well as on the brain (JURNA and BRUNE, 1990). In the brain COX-1 is present under inflammatory conditions and in the spinal cord nociceptive processes are mainly influenced by COX-2 (VANE et al., 1998; VANEGAS and SCHAIBLE, 2001).

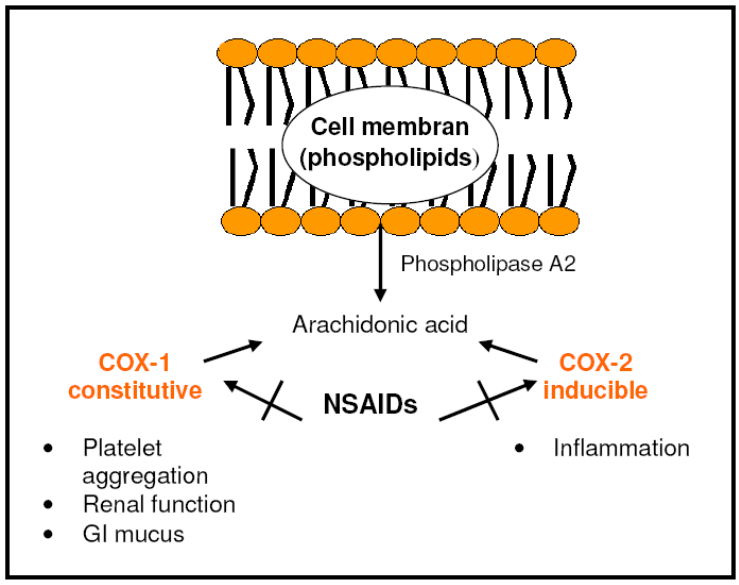

Figure 5: Representation of cyclooxygenase activity. COX-1 is constitutively expressed while COX-2 may be present by inflammatory processes (WOLFE et al., 1999).

4.2.2.1.2. Nitric oxide synthase and COX inhibitors

Recently, another mechanism of action of this class of drugs has been investigated. Regardless of their COX selectivity, some authors believe that the nitric oxide (NO)-cyclic guanylate monophosphate (cGMP) pathway plays an

important role for the induction of analgesia. It was shown that the antinociceptive action of several NSAIDs was reverted by the application of NO synthase inhibitors (L-NAME) and guanylate cyclase inhibitors (methylene blue) (DESOKY and FOUAD, 2005). Nitric oxide is a chemical messenger in a multitude of biologic systems, having homeostatic activity in the maintenance of cardiovascular tone, platelet regulation, and central nervous system signalling, as well as a role in gastrointestinal smooth muscle relaxation, and immune regulation. NO may be one of the oldest biological molecules on earth and is synthesized by cell-specific isoforms of NO synthase (NOS) from the amino acid L-arginine. NOS has been broadly classified into a constitutive (cNOS) and an inducible (iNOS) subtype. The constitutive isoform is calcium- and calmodulin-dependent, continuously expressed, and produces NO in picomolar concentrations. iNOS in contrast is calcium-independent and requires inducers such as specific cytokines or endotoxin for its expression (SCHROEDER and KUO, 1995; ELPHICK and SCHLEIFFER, 1997). There are a lot of findings supporting an important role of the activation of the L-arginine-NO-cGMP pathway for antinociception. Not only in the periphery but also within the central nervous system it is possible to see a direct relation between acute hypernociception blockade and the stimulation of the L-arginine-NO-cGMP pathway (KNOWLES et al., 1989; DUARTE et al., 1992; SACHS et al., 2003).

4.2.2.1.3. Endogenous opioid system

Evidence clearly shows that not all NSAIDs act in the same way. COX inhibition may be one of the most investigated mechanisms of these anti-inflammatory drugs, but several studies suggest different antinociceptive pathways in the periphery that even involve the endogenous opioid system. DROGUL et al (2007) found that metamizole administered in the periphery causes antinociception probably through opioidergic mechanisms, since the application of naloxone reverted its effect. Naloxone pretreatment had no effect on the antinociceptive effects of other NSAIDs like diclofenac or ketorolac, suggesting differences in the mechanism of action among the NSAIDs. At the level of the brainstem the NSAIDs induce antinociception by activating the so called “descending pain-control system”. This system is also activated by exogenous and endogenous opioids supporting the theory of a common pathway in the mechanism of action between both analgesics (VANEGAS and TORTORICI, 2002). Opioids like

fentanyl also reverse prostaglandin-induced hyperalgesia, probably by activating opioid receptors at the periphery or via the L-arginine/ nitric oxide/ cyclic-GMP pathway (MAEGAWA and TONUSSI, 2003). A similar mechanism of action can be seen with some NSAIDs (DESOKY and FOUAD, 2005). Although NSAIDs do not have a direct effect on the spinal cord, their analgesic action appears to be spinally mediated by activating inhibitory descending opioidergic mechanisms (LIZAGARRA and CHAMBERS, 2006). This means that a combination of opioids and NSAIDs leads to potentiation of the analgesic effects of both drugs (SHUG 2007). The potentiation has been experimentally and clinically approved in several studies (VAUGHAN et al., 1997; BERGMANN et al., 2007; RICHTER, 2007; LÓPEZ-MUÑOZ et al., 2008).

4.2.2.2. COX selectivity

Based on the nature and physiological actions of COX-1 and COX-2, the NSAIDs that preferentially block the production of COX-2-related PGs may be clinically superior to those with less COX-2 selectivity. Selective COX-2 inhibitors may be more desirable, because they inhibit the formation of PGs responsible for the clinical signs associated with inflammation, whereas their effect on COX-1 and its homeostatic properties is minor (CURRY and COOK, 2005). However, recent studies showed that the inhibition of COX-1 and not COX-2 mimics the action of the NSAIDs in the PAG (LEITH, 2007). Emerging information supports a role for COX-2 in the stomach having an impact on the gastrointestinal (GI) safety of COX-2-selective NSAIDs. COX-2 induction has been documented in Helicobacter pylori gastritis, inflammatory bowel disease, and bacterial infections of the gastric mucosa; thus, administration of COX-2 inhibitors in presence of GI inflammation may be harmful (TERRENCE, 2006). In a study by REUTER et al. (1996) the administration of selective COX-2 inhibitors to a rat model of colitis significantly inhibited the mucosal PG synthesis and notably increased colonic damage. In another study by LASCELLES et al. (2005) 69% of dogs treated with deracoxib, a selective COX-2 inhibitor, died or were euthanized because of GI tract perforation. However, all of them had received deracoxib at higher than recommended dosages or had received at least one other NSAID or glucocorticoid. Anyway, an important role of COX-2 in regulating ulcer healing has been demonstrated, and it is possibly mediated via PGD_2 synthesis (PERINI and WALLACE, 2003; ZAMUNER et al., 2003) Taken together, COX-2 seems to

be required for GI defence, and ulcers may result from the inhibition of both enzymes (TERRENCE, 2006).

4.2.2.3. NSAIDs drugs

4.2.2.3.1. Carprofen

Carprofen (Rimadyl®), a propionic acid derivate, was the first COX-2 selective drug approved for use in dogs. It is available in oral and injectable forms. The COX-2 selectivity of carprofen renders the oral form effective for long- and short-term pain management. The primary difference in pharmacokinetics between the oral and injectable forms is their peak plasma concentration after drug administration: a single subcutaneous injection of carprofen results in a lower peak plasma concentration than the oral administration of the same amount. Like other NSAIDs, carprofen is highly protein bound in the blood, and it undergoes hepatic metabolism. Much of the drug is eliminated in the faeces (60% to 75%) and the remaining amounts are eliminated in the urine (CURRY and COOK, 2005).

Long-term oral administration of carprofen, compared with other NSAIDs, appears to have fewer GI side effects, possibly due to sparing the COX-1 isoenzyme (LUNA et al., 2007). However, as mentioned, GI signs have been reported in some animals, thus monitoring for adverse effects must be performed when this drug is used. Carprofen is mainly indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopaedic procedures in dogs (CURRY and COOK, 2005; TERRENCE 2006). The administration of carprofen for 28 days in dogs with osteoarthritis constituted a successful therapy without adverse effects, since the lameness score, measured on visual analogue scale, reduced significantly after treatment (2 mg kg^{-1} per day) (LIPSCOMB et al., 2002). Another study investigates the long-term use of carprofen (85 days) in dogs with chronic osteoarthritis and according to the veterinarians' and owners' assessments the results showed a 70% effectiveness of therapy (dogs free from lameness or signs less pronounced). The authors proposed that this percentage might be higher if the condition of the animals would have been recognized and treated earlier. Dogs suffering from chronic pain may require longer periods of treatment (MANSA et al., 2007). However, the administration of a different NSAID (firocoxib) clinically

showed a greater amelioration of the lameness associated with osteoarthritis in dogs compared to carprofen (POLLMEIER et al., 2006).

After moderately painful surgery, the administration of full μ opioid agonists provides significantly better post-operative analgesia than carprofen. However, the widely recognized adverse effects of opioids may preclude the use of these agents (SLINGSBY, 2006). It has been shown that the sole use of NSAIDs (meloxicam or carprofen) might be effective in relieving pain after orthopaedic and soft tissue surgery (NOLAN AND REID, 1993; LASCELLES et al., 1998; GRISNEAUX et al., 1999; LAREDO et al., 2004; LEECE et al., 2005). Other authors recommend a balanced analgesic protocol and prefer a combination of local anaesthetics, systemic opioid agonists and carprofen, providing a safe and effective postoperative pain control after canine fracture repair (BERGMANN et al., 2007). Carprofen may prevent the inflammatory hyperalgesia and its combination with anti-hyperalgesic opioids like buprenorphine prevents the development of hypersensitive states after injury (TAYLOR et al, 2007). In the case of moderate pain (e.g. ovariohysterectomy) analgesia provided by the use of the NSAID meloxicam was shown to be clinically comparable to that of butorphanol (CAULCKET et al., 2003)

4.2.2.3.2. Sodium Metamizole

Sodium metamizole (Dipyrone, Vetalgin®) is a non-opioid analgesic derived from the pyrazolones with antipyretic and anti-inflammatory properties available as oral, rectal and injectable formulation. In aqueous solution metamizole is immediately hydrolysed to 4-methyl-amino-antipyrine (MAA), which is further metabolized to 4-amino-antipyrine (AA), 4-formyl-amino-antipyrine (FAA) and acetyl-amino-antipyrine (AAA). Of these four major metabolites, MAA has been demonstrated to be the pharmacologically active compound (VLAHOV et al., 1990). After oral administration, metamizole is non-enzymatically hydrolyzed in the intestine and is rapidly and almost completely absorbed (ZYLBER-KATZ et al., 1992), its metabolites reaching maximal serum concentration in 1.5-2 hours in dogs (VOLZ and KELLNER, 1980). All metamizole metabolites are preferentially eliminated via urinary tract (VOLZ and KELLNER, 1980). The plasma protein binding of metamizole metabolites is relatively low; a higher binding affinity is observed for MAA and AA than for FAA and AAA (ZYLBER-KATZ et al., 1985). Metamizole metabolites can cross the haematoencephalic

barrier (COHEN et al., 1998).

Metamizole, like a lot of NSAIDs, may exert its effect on inflammatory pain through the inhibition of PG synthesis in both peripheral and central nervous system (CHANDRASEKHARAN et al., 2002). However, because metamizole is antipyretic and has little or no anti-oedematous effect, a central site of action may be highly implied. However, LORENZETTI and FERREIRA (1985) suggest only a peripheral action of metamizole and this may result from direct and dose-dependent blockade of hyperalgesia rather than from prevention of the release of PGs in inflamed tissue. This can be explained with the findings of PIERRE et al. (2007), who suggest that the pharmacologically active metabolites of metamizole inhibit COX activity by sequestering radicals which initiate the catalytic activity of this enzyme. In the same study the data confirm an unlikely competition of MAA with arachidonic acid, as known to occur with traditional NSAIDs. REZENDE et al. (2008) also propose a peripheral both anti-hyperalgesic as well as a hypoalgesic action of metamizole. Although they insist in the involvement of COX activity, they could not prove the inhibition of PG biosynthesis as a direct cause of analgesic action of metamizole. In contrast with these studies, HINZ et al. 2007 found a pronounced inhibition of both COX-1 and COX-2 enzymes after oral administration of recommended doses of metamizole to humans. At therapeutic concentrations, a selective peripheral blockade of COX-2 has been described. This supports the view that a significant portion of metamizole´s analgesic action may be due to peripheral mechanisms (CAMPOS et al., 1999).

On the other side, a central antinociceptive action of metamizole is attributed to the inhibition of central COX-3 leading to a reduced PGE2 concentration in the hypothalamic region. Despite being potent COX-3 inhibitors in cultured cells, many other NSAIDs are unlikely to reach comparable effective cerebral concentrations due to their highly polar structure (BOTTING and AYOUB, 2005). COX-3 inhibition and a resultant decrease of elevated cerebral PGE2 concentrations in hyperthermic patients has also been proposed to be the major mechanism for acetaminophen's antipyretic action (AYOUB et al., 2004), and the same may be true for metamizole.

The analgesic properties of metamizole in the CNS may not only be due to its capacity to inhibit COX isoforms. Several studies support the involvement of descending pathways in the brainstem. CARLSON and JURNA (1987) provided

further evidence that metamizole produces a central antinociceptive and analgesic effect by stimulating spinal inhibition from the PAG. Moreover, they show that the supraspinal activation of descending pathways by metamizole can be potentiated by the spinal inhibitory action of morphine. Later, LORENZETTI and FERREIRA (1996) address the metamizole-mediated antinociception as a combined peripheral and spinal effect. Since the analgesic action of metamizole could be abolished with the application of L-NMMA (a nitric oxide synthase inhibitor) or methylene blue, it was proposed that its analgesic action results from the stimulation of the L-arginine/cGMP pathway. These findings also support a potentiating effect of metamizole in the antinociceptive action of opioids (SONG et al. 1998). Other mechanisms which involve the opioid nociceptive control system have been investigated. In one study of TORTORICI and VANEGAS (1993), the microinjection of metamizole in the PAG of the rat resulted in antinociceptive responses in different tests, confirming a direct action of this NSAID on the PAG and providing evidence of involvement of medullary OFF- and ON-cells in such an antinociceptive effect. Newer findings of TORTORICI et al. (1996) support the theory of medullary OFF- and ON-cells. The administration of metamizole may stimulate the liberation of β-endorphins and its analgesic effect may be reverted by naloxone, suggesting that endogenous opioids are partly responsible for the antinociceptive action of metamizole. VAZQUEZ et al. (2005) also found an activation of the endogenous opioidergic circuit along the descending pain control system. This action may be mainly centrally mediated through the inhibition of nociception in spinal dorsal WDR neurons.

On the other side, a peripheral action of metamizole associated with the activation of ATP-sensitive K^+ channels has been described. This possibly involved the stimulation of the L-arginine/NO/cGMP pathway in sensory neurons, a mechanism also seen in opioid analgesia (ALVES and DUARTE, 2002) Interestingly, BEIRITH et al. (1998) refuse an association of ATP-sensitive K^+ channel activation and the antinociceptive effect of metamizole, since the administration of glibenclamide (K^+ channel blocker) did not significantly modify metamizole's antinociceptive effect. In the same study L-arginine and naloxone failed to antagonize metamizole´s antinociceptive action, denying the activation of the L-arginine/NO/cGMP and the opioidergic system as one of the analgesic mechanisms of metamizole. The authors propose a modulatory effect on

glutamate-induced hyperalgesia as well as an interaction with glutamate binding sites.

Despite the numerous behavioural and electrophysiological studies that have been performed, the mode and site of action of metamizole still remain controversial.

Metamizole does not posses the same adverse effect as common pyrazolones at clinical doses. At doses of 300 mg/kg SID metamizole may provoke salivation, emesis, and weight loss due to reduced food intake. After a 4 weeks' therapy of 450 mg/kg SID serum values for BUN and alkaline phosphatise (ALP) were found to be elevated in the dog. However, no gastric ulceration was observed and a carcinogenic effect was only seen with the pyrazolone aminopyrine (KRAMER, 1980). The administration of different doses of metamizole to the rat did not produce gastric mucosal injury compared with other NSAIDs like diclofenac (SÁNCHEZ et al., 2002a). In the same study the authors proved that gastric PGE_2 levels decreased in both groups similarly, suggesting that this diminuition of PGE_2 production may not be the only mechanism of damage. SÁNCHEZ et al. (2002b) also investigated the tolerability of metamizole and acetaminophen compared with diclofenac and found that unlike metamizole and acetaminophen, under diclofenac treatment blood loss, anaemia, and even impaired kidney function are observed. An endoscopic assessment in adult human volunteers has also been undertaken, and the administration for two weeks has shown effects on gastroduodenal mucosa comparable to those of paracetamol and placebo. Metamizole showed a great gastrointestinal tolerability and this fact is of particular value in the treatment of patients in whom NSAID are contraindicated (BIANCHI, 1996). The reason why metamizole does not produce gastric ulceration is still unknown. It is believed that its antispasmodic effect on vascular smooth muscle may increase the blood flow in the responsible tissues (ERGÜN et al., 2001). GÜLMEZ et al. (2008) found that metamizole increases the blood flow of arterial dorsal skin flaps in comparison with diclofenac in the rat. This relaxing effect of metamizole may be produced by an active nonenzymatic degradation product and it seems likely that 4-methylaminoantipyrine is the principle compound that leads to the observed relaxation. It is believed that the activation of the Na-K-ATP_{ase} pump may lead to this effect since the blockade with ouabain, a Na-K-ATP_{ase} pump inhibitor, inhibited the relaxation response of metamizole (ERGÜN et al., 1999).

There is little information of metamizole's clinical efficacy in the dog. It is not used very frequently in small animal practice, whereas in equine medicine metamizole is often administered to treat colic pain and fever (ROBERTS and MORROW, 2001). In human medicine it is one of the most used analgesics to treat postoperative pain, acute pain, referred pain and migraine (EDWARD et al., 2008). During mastectomy and retina surgery in humans metamizole and paracetamol have demonstrated similar analgesia (LANDWEHR et al., 2005; KAMPE et al., 2006). TORRES et al. (2001) found that metamizole and tramadol result in a similar pain relief after abdominal surgery in humans. Other authors failed to find good results with metamizole when compared with other NSAIDs like meloxicam or diclofenac, or opioids like tramadol (CANDER et al., 2005, YILMAZ et al., 2006). Metamizole appears to be a synergic analgesic in several studies: it improves the activity of other antinociceptive drugs and may even have a sparing effect. In an experimental rat model, LOPEZ-MUÑOZ et al. (2008) demonstrated an optimal morphine and metamizole combination. Both drugs produce a potentiation of their antinociceptive effects during intense pain. RICHTER (2007) found a marked intra-operative opioid-sparing effect during total hip replacement surgery in the dog.

5. Pain evaluation

5.1. Subjective methods

The importance of providing good pain management in veterinary medicine is increasing substantially. However recent studies on the perioperative provision of analgesia in the small animal practice suggest that it is still suboptimal (LASCELLES et al., 1995). Pain recognition in the veterinary profession is problematic because animals are unable to verbally express their feelings and therefore the veterinarian must observe and interpret the animal's behaviour and physiological changes as good as possible (BIANCHI et al., 2003). HANSEN et al. (1997) found that physiological parameters do not change significantly after ovariohysterectomy in dogs and that compared to the measurement of heart rate and respiratory rate measurement of cortisol may be more accurate. In contrast, FOX et al. (1998) found that the intravenous application of butorphanol before ovariohysterectomy did not reduce the cortisol response after surgery. In fact, several studies have been performed on this topic and none of them could find a

direct relation between pain and increased values of cortisol in clinical settings, mainly because of the stress component. Plasma cortisol concentrations have failed to provide a useful measure under clinical conditions (MORTON and GRIFFITHS, 1985; FIRTH and HALDANE, 1999; REESE et al., 2001; SLINGSBY et al,. 2006; BERGMANN et al. 2007; EGGER et al,. 2007). On the other side pain indicators like respiratory rate, heart rate, blood pressure or increased body temperature are the most cited in the literature but there are few works that validate them (MORTON and GRIFFITHS, 1985). HOLTON et al. (1998b) found that respiratory rate and heart rate are not useful indicators of pain in hospitalised dogs. They used a subjective numerical rating scale (NRS) and correlated both subjective and objective data without satisfactory results. Because the individual conception and understanding of pain has a high variability between evaluators, observer variability must be taken into account when more than one observer is used. Besides the numerous scales used to asses pain lack validation (HOLTON et al., 1998a; HANSEN, 2003). The development of a scale to measure pain in animals is challenging, but the combination of behavioural and physiologic parameters seems to be useful and reliable to evaluate pain in dogs and their response to analgesics during the postoperative period. However, more studies will have to be done (FIRTH and HALDANE, 1999). Nowadays, most investigators use a combination of subjective observations (posture, activity, movements, and attitude) and objective measurements (respiratory rate, heart rate, pupil dilation, and body temperature) to evaluate pain in animals. All these observations are also useful for pain scoring on a visual analogue scale (VAS) (fig. 6). This scoring system consists of a 10 cm line, with 0 mm representing no pain and 100 mm the worst pain imaginable (BRODBELT et al., 1997; DENEUCHE et al., 2004; SLINGSBY et al., 2006).

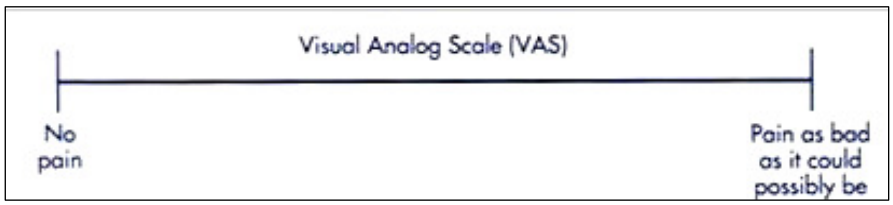

Figure 6: Visual analogue scale (VAS)

5.2. Objective methods

A lot of attempts have been made to validate the utilization of an objective device to measure pain. The most frequently mentioned device is a pressure algometer, which basically consists of a pressure nociceptive threshold test. Studies in cats and dogs not undergoing surgery have shown good results and greater precision than thermal stimuli to asses pain threshold after administration of butorphanol, buprenorphine or carprofen (ROSA and MASSONE, 2005; DIXON et al., 2007; TAYLOR et al., 2007). A similar algometer has been used in cats given pethidine after castration and the results suggest that it could become useful to asses the effectiveness of analgesics agents (SLINGSBY et al., 2001). An alternative device commonly used in human medicine to test pain responses are the "Von Frey" monofilaments. "Von Frey" monofilaments are used to estimate tactile sensibility and with increasing bending force, the filaments will excite skin nociceptors and may determine tactile pain thresholds. In veterinary medicine they have been used to evaluate the analgesic effects of morphine in dogs (KUKANICH et al. 2005). Also exerting pricking pain this method is useful to determine primary and secondary hyperalgesia in humans (HARDY et al., 1950; CERVERO et al., 1993). In a study by KEIZER et al. (2007) "Von Frey" thresholds showed a good clinical correlation with the results of a NRS. Unfortunately in veterinary medicine dogs and cats often react before a painful stimulus has been evoked rendering this method unreliable for the estimation of pain in animals (BERGMANN et al., 2007).

5.2.1. Force plate analysis

After limb surgery animals usually do not show a normal gait and frequently go lame. This may be due to a functional abnormality, but it normally occurs because of pain after surgery and the intent to avoid long lasting contact to the ground (indirect parameter of pain) (BUDSBERG et al., 1999). The human eye is not able

to capture the complexity of limb movements making an intra- and interindividual evaluation extremely difficult and, therefore, a visual grading of joint lameness might be limited (KOSFELD, 1996; BUDSBERG et al., 1996). Increasing interest in the biomechanics of motion has brought together various methods of analysis, including force plates, electrogoniometry, and cinematography. Being a useful non-invasive method to objectively determine the degree of postsurgical pain in dogs, the gait analysis has been used extensively to examine the gait and gait-associated abnormalities, as well as the success of various modes of therapy (BUDSBERG, 1987; BENNETT et al,. 1996; EVANS et al., 2005). This system provides reliable information on the kinematic of the patient, as well as a precise analysis of the load distribution (kinetic) (MANLEY et al., 1990; ALLEN et al., 1994; BERTRAM et al., 1997). Normally, 60% of a dog's body weight is placed on the forelegs and on the hind legs only 40% (ROY, 1971). In a healthy dog the load should be regularly distributed so that each foreleg bears 30% and each hind leg 20%. This relation is described in stance but it also remains in movement (BUDSBERG et al., 1987) and it may be altered by patients with orthopaedic problems due to an animal's tendency to avoid support on the injured leg (ROY, 1971).

The locomotion of the dog is described as a dynamic process, where the same pattern of movement occurs repeatedly in a cyclic sequence (DeCAMP et al., 1993). As mentioned above, this dynamic process can be classified into kinetic or kinematic analysis. The measurement methods for the kinetic and the kinematic events are dynamometry (ground reaction force) and the kinemetry (motion analysis) respectively (OFF and MATIS, 1997). The dogs are analysed during walk or trot; the gait contains phases in which 2 or 3 legs are in contact with the ground, whereas in trot only two legs touch the ground at the same time (DeCAMP, 1997).

5.2.1.1. Kinetic

The kinetic is defined as the observation of the relation between a body's movement and the corresponding forces (DeCAMP, 1997). The system measures the ground reaction force exerted during the stance of a gait. For better comparison between experimental protocols the ground reaction forces (GRF) are expressed in percent in relation to body weight (BW) (HUTTON et al., 1969). Later BUDSBERG et al. (1987) described the ground reaction forces (GRF) of

healthy dogs and expressed them in terms of vertical, craniocaudal and mediolateral vectors, Fz, Fy and Fx, respectively (fig. 7). Peak magnitude, duration and impulse in normal and pathological animals have been examined by measurement of vertical GRF (BUDSBERG, 1995).

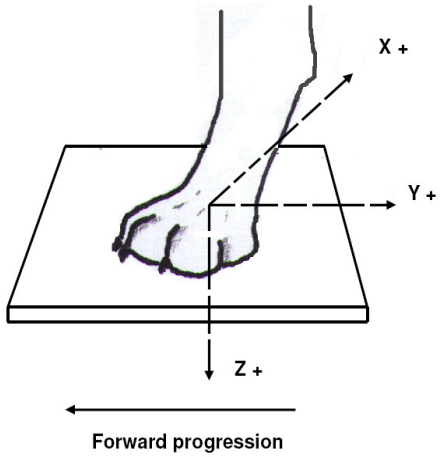

Figure 7: Direction of the ground reaction forces (GRF) in healthy dogs. Fz = vertical GRF, Fy = craniocaudal GRF and Fx = mediolateral GRF (extracted from BUDSBERG et al., 1987).

The magnitude of the vertical GRF depends in part on the velocity of the locomotion (RIGGS et al. 1993). During walk this accounts for approximately 55-70% of the animals BW and increases to 97-117% during trot (BUDSBERG et al., 1987; HUTTON et al., 1969; JEVENS et al., 1993; DeCAMP 1997). The vertical GRF (Fz) is the greatest force compared to the craniocaudal and mediolateral forces and thus it is the most reliable and reproducible of all. The maximal vertical GRF (peak Fz) during stance is linearly related to morphometric data like length of humerus or femur, size of the paws or bodyweight. BUDSBERG et al. (1987) described values of peak forces up to 70% of the animals BW on the forelegs and up to 50% of their BW on the hind legs. The load distribution can also be calculated and is defined as a quotient.

Another parameter that may be evaluated is the vertical impulse. The impulse is the force integral over a determined time, which means the total force that is applied during the stance phase (BUSBERG et al., 1987). The course of the vertical GRF can be divided in two intervals: the loading interval and the

unloading interval (fig. 8). It is interesting to know how rapidly a limb loads (severity of impact) and how long a limb accepts load. These data may provide additional specific information of limb function. Both parameters, severity of impact and acceptance of load, are measured in % BW per second or Newton (N) per second (BUDSBERG et al., 1995).

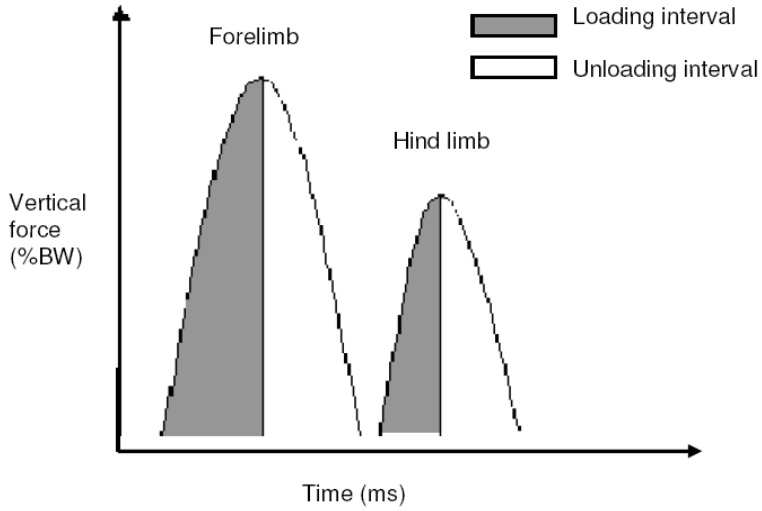

Figure 8: Vertical force signals of the forelimb and the ipsilateral hind limb of a dog at a trotting gait, separated into the loading and the unloading intervals (BUDSBERG et al., 1993).

The most common protocol consists of the dog being led on a leash by a handler on a platform containing force plates, but FACHON et al. (2006) proposed a modification of the traditional protocol by using a treadmill equipped with force sensors. This allows keeping the velocity constant and permits the simultaneous measurement of all limbs and assures a steady sequence throughout the entire recording process (OFF, 1992; KOSFELD, 1996; OFF and MATIS, 1997). As mentioned earlier this system provides reliable information about the gait and its features. A lot of studies have been made in order to validate different medical therapies. In one study of POY et al. (2000) healthy dogs and dogs with hip dysplasia were compared. The authors discovered a significant difference in the range of motion of the coxofemoral articulation between groups. The success of canine hip dysplasia treatment could also be evaluated through this method. After

triple pelvic osteotomy, the operated dogs transmitted significantly greater force than non-operated patients (McLAUGHLIN et al., 1991). MANLEY et al. (1990) also documented the success of cementless versus cemented total hip replacement in dogs. Within three months both groups returned to their preoperative ground reaction force levels on the implanted hind limb. For better comparison the authors propose the analysis of load distribution, because the cementless group showed a disparate load distribution between the operated and non-operated limb, whereas the cemented group demonstrated equal load distribution in both hind limbs. Normally, the vertical forces are reduced greatly after total hip replacement in dogs compared with preoperative values but they return to normal values in magnitude and pattern after four months (DOGAN et al., 1989). Similar results were found by BUDSBERG et al. (1996) in a prospective study of dogs undergoing unilateral total hip replacement. Loading rates increased over the study period indicating willingness to load the operated hip. They also compared subjective lameness scores and objective GRF and found that the visual grading of coxofemoral joint lameness is limited.

III. OBJECTIVES

The analgesic and anti-inflammatory action of NSAIDs in the periphery has been proven to be satisfactory compared to opioids in a lot of orthopaedic and soft tissue surgeries in animals (LAREDO et al., 2004; LAFUENTE et al., 2005; SLINGSBY et al., 2006). Even though NSAIDs do not always eliminate the need for supplementary analgesia during the postoperative period its use reduces the postoperative requirements for opioids (PIBAROT 1997; HELLYER et al. 1999). A combination of opioids and NSAIDs like metamizole or acetaminophen delivers satisfactory analgesia and, additionally, may reduce the adverse effects seen with opioids like morphine or tramadol (RAWAL et al., 2001; GEHLING AND TRYBA, 2008).

Despite the fact that the author of this study believes that adequate pain relief is best achieved through the combination of several analgesics drugs, dogs included in this study received either metamizole or carprofen during the postoperative period. The aim of the application of only one analgesic drug was to evaluate the analgesic effect of metamizole as a sole agent compared to carprofen after orthopaedic surgery in dogs.

In summary the objectives of this study are:

- To evaluate the analgesic effect of recommended dosages of metamizole after canine total hip replacement.
- To compare the analgesic effect of metamizole to that of recommended dosages of carprofen after canine total hip replacement.

IV. MATERIAL AND METHODS

1. Patients

Thirty-nine dogs weighing between 5.5 and 60.5 kg (no breed specificity) were included into this study. These animals were admitted to the small animal clinic for surgery and gynaecology of the Ludwig-Maximilians-University, Munich for an elective total hip replacement (THR). Dogs were only included into the study, if the clinical examination and results of the haematological and biochemical blood analysis revealed no abnormalities. Hence all animals were classified as low anaesthetic risk patients (ASA I/II). The dogs who presented any other pathology of the locomotion except for a coxarthrosis and patients who were previously treated with any other analgesics except nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded. Owner approval was obtained before a dog entered the study. Dogs were housed and treated as clinical patients during the study period.

2. Anaesthesia and analgesia

Food was withheld for approximately 8 hours before induction of anaesthesia. Water was available ad libitum until shortly before premedication. All anaesthetic procedures were performed by the same anaesthetist (AS). After a clinical examination patients were premedicated with an intramuscular injection of 20 $\mu g \cdot kg^{-1}$ acepromacin (Vetranquil® 1%, A. Albrecht GmbH & Co.KG, Zurich, Switzerland). Twenty minutes later an appropriately sized intravenous catheter was placed into one cephalic vein and induction of anaesthesia was then performed with 4 – 7 $mg \cdot kg^{-1}$ propofol IV (PropoFlo Vet® 1%, A. Albrecht GmbH & Co.KG, Aulendorf, Germany). After intubation of the trachea the animals were connected to a mechanical ventilator (Fabius Tiro, Dräger, Lübeck, Germany) and anaesthesia was maintained with isoflurane (Isoba®, Intervet, Unterschleißheim, Germany) (et1.5 vol.%) in an oxygen/air (50/50) mixture. During surgery a crystalloid infusion (Tutofusin, Baxter GmbH, Unterschleißheim, Germany) was administered at 10 $ml \cdot kg^{-1} \cdot h^{-1}$. Analgesia was achieved with a bolus of 2 $\mu g \cdot kg^{-1}$ of fentanyl IV (Fentanyl-Janssen®, Janssen, Neuss, Germany) given on the induction of anaesthesia followed by a continuous rate infusion (CRI) between 5 – 20 $\mu g \cdot kg^{-1} \cdot h^{-1}$ depending on the hemodynamic

parameters during the surgery. For perioperative infection prophylaxis, 20 mg·kg^{-1} of lincomycin (Albiotic® AD.US.VET 300 mg, Pfizer GmbH, Karlsruhe, Germany) was intravenously administered after the induction of anaesthesia. Anaesthetic monitoring included electrocardiography, capnography, pulse oximetry, non invasive measurement of blood pressure, as well as measurement of body temperature.

3. Surgery

The operation was performed according to the modified method described by HOHN et al. (1986). After shaving and disinfection of the operating limb, dogs were placed in lateral recumbency. The approach to the hip joint was performed from craniolateral and through cranial mobilization of the m. tensor fasciae latae and partial tenotomy of the tendon of the m. glutaeus profundus. After dissection of the joint capsule, the femoral head was dislocated and then removed by osteotomy. Subsequently, the articular surface was prepared to allow the implantation of the prosthesis. The acetabulum prosthesis was implanted with 10 g methylmetacrilat, which normally hardens after 10 minutes. Following this the femur was prepared and 40 g cement was introduced from distal to proximal to implant the femur prosthesis. After hardening of the cement the artificial head was put on the femur prosthesis and then placed into the acetabulum. Finally the joint capsule was closed, the tendon of the m. gluteus profundus was reinserted and the wound was sutured. Upon completion of the surgery all patients were radiographically controlled and brought to the intensive station for recovery.

4. Study design

The study was conducted as a prospective, blinded and randomized clinical trial. After admission to the hospital, dogs were scheduled for surgery the following day. Patients were allocated to one of two groups, group C or group M. Dogs in group C (n=20) preoperatively received 4 mg·kg^{-1} of carprofen (Rimadyl®, Pfizer GmbH, Berlin, Germany) IV. For the following two days animals received the same dose of carprofen once daily. Animals in group M (n=19) received 50 mg·kg^{-1} of sodium metamizole (Vetalgin®, Intervet GmbH, Unterschleißheim, Germany) IV at the end of surgery. Metamizole treatment was repeated every six hours on the day of the surgery and every eight hours on the following two days.

5. Pain assessment

5.1. Pain scores

All pain assessments were performed by one evaluator (AS). Three systems were used: a visual analogue scale (VAS) (fig. 6), a modified Melbourne pain scale (mMPS) (appendix 1) and force plate analysis. VAS is a subjective way to assess pain and consists of marking on a 100 mm line, labelled at one end "no pain" and with "very severe pain" at the opposite end. The observer has to place a mark on the line that corresponds to the pain intensity of the animal. The mMPS used for this study is based on eight variables considered to be relevant for pain assessment in previously published studies (PIBAROT et al., 1997; HOLTON et al., 1998; DENEUCHE et al., 2004; LAREDO et al., 2004; HOELZER et al., 2005): relative increase in heart rate, relative increase in respiratory rate, response to palpation of the injured/ operated area, vocalization, the animal's activity and posture as well as the response to manipulation and to leading the animal out of the kennel. The mMPS consisted of firstly observing the animal's behaviour while alone and undisturbed in its kennel. This allowed describing the patient's activity and posture. Then the evaluator measured respiratory rate which was difficult on many occasions due to the dogs' tendency to pant. In these cases the parameter "respiratory rate" was not considered for the evaluation. Next, the heart rate was counted by feeling digital palpation of the femoral pulse. Here it was very important to avoid unnecessary contact with the dogs in order to prevent patients to become excited. Once finished, the evaluator carefully touched around the wound and waited for a reaction. Then, the operated leg was passively mobilized waiting for a reaction, too. Finally, the dog was led on a leash out of the kennel to evaluate the degree of lameness. All of these observations were also performed for the visual analogue scale measurement.

The pain score was obtained by summation of the scores given to the selected variables and ranged from a minimum value of 0 to a maximum of 24. Both scales were used for pain assessment 3, 6, 9, 12, 20, 24, 28, 32, 36, 44, 48 and 56 hours after the end of surgery (T_0, T_3, T_6, T_9, T_{17}, T_{21}, T_{25}, T_{29}, T_{33}, T_{41}, T_{45} and T_{53} respectively). The first evaluation was made three hours after the end of surgery. This was achieved approximately 2.5 hours after extubation in all patients. Once

the patients were extubated, a brief pain evaluation was made to ensure the patients' wellbeing and during the next hours they were under observation of a veterinarian and/or a technician. If a dog showed signs of pain before T_0, the evaluator (AS) was called to score the animal's pain by means of VAS and mMPS. If the VAS or mMPS scores reached values of or above 50 or 12, respectively, rescue analgesia was immediately provided. It was administered intravenously and consisted of 10 $\mu g \cdot kg^{-1}$ of buprenorphine (Buprenovet®, Bayer AG, Leverkusen, Germany). Dogs that received rescue analgesia were excluded from their group and the statistical analysis but pain evaluation was continued.

5.2. Force plate analysis

In order to evaluate the degree of lameness, all patients were subjected to a force plate analysis, once preoperatively (preOP) and then on the first (OP1) and second postoperative day (OP2). The examinations of all dogs were done in the same room and by the same person (AS). In the centre of this room a podium (approx. 5.7m long, 1.2m wide and 28cm high), which holds the treadmill, has been built. The treadmill is made up of two parallel belts, which are visible over a length of 140cm and a width of 80cm. Four kistler force plates (70cm length and 40 cm width) lie under these two belts. The force plates are connected to a computer via an amplifier and a signal transducer. Fine tuning of the treadmill's speed is possible to 0.02 $m \cdot s^{-1}$. The speed in this study was set according to the patient's acceptance, but variability between dogs was avoided.

The measurement of ground reaction forces took place at 1000 Hz. After recording, all data were then exported to an ASCII-file. Steps with correct first ground contact, and steady and regular pace were selected by proprietary Software. Then the kinetic results were distributed and saved in numeral and graphical form.

For this study, only peak vertical force (PVF) and vertical impulse (VI) were considered. To reduce variability only the data of the hind legs were analysed. All dogs were subjected to preoperative analysis (preOP), and then on the first and second day after surgery, respectively. The values of the contralateral (not operated) hind limb (nop) were considered as 100% each day and the percentage of the operated limb (op) respective to nop were calculated for dogs in group M and C. These results were compared and analysed statistically for preOP, OP1 and

OP2. Differences between preOP, 1OP and 2OP for each group were also compared and analysed statistically.

6. Statistical analysis

Weight, age, surgery time, anaesthesia time, amount of intraoperatively administered fentanyl as well as treadmill velocity were statistically analysed with the Man Whitney Test, SPSS 17.0. Results of pain scores (VAS, mMPS) were analysed with the same test. Data obtained on the treadmill were analyzed with a T-test. The level of significance was set at $p \leq 0.05$.

V. RESULTS

Thirty-nine dogs (no breed specificity) with a mean body weight of 32.7 $\pm$ 9.8 kg BW (5.5 kg to 60.5 kgBW) and with a mean age of 4.2 + 3 years (8 months to 12.3 years) were enrolled in this study. Twenty dogs received carprofen (4 $mg \cdot kg^{-1}$) once daily and nineteen dogs received sodium metamizole (50 $mg \cdot kg^{-1}$) three times a day. Ten dogs (25.6%) were intact males, nine (23.1%) were intact females, nine (23.1%) were castrated males and eleven (28.2%) were spayed females (table 1).

Table 1: Gender distribution in the groups

Sex	Metamizole	Carprofen	Total
Male	7	4	11
Female	4	5	9
Neutered male	5	3	8
Spayed female	3	8	11
Total	19	20	39

Twenty dogs (51%) were operated on the left leg, ten in group M and ten in group C. Nineteen dogs (49%) were operated on the right leg, 10 in group C and nine in group M (table 2). No statistical differences were seen in age, body weight, duration of anaesthesia, duration of surgery and intraoperative fentanyl requirements between groups (table 3).

Table 2: Data of the patients

N°	Race	Group	Weight (kg)	Age (months)	Indication of Surgery	Side
1	Labrador	M	34	55	severe bilateral coxarthrosis	Right
2	Labrador mix	M	37.5	100	severe bilateral coxarthrosis	Right
3	German shepherd	M	36	16	mild bilateral coxarthrosis	Right
4	Golden retriever	M	26	10	hip dislocation and mild bilateral coxarthrosis	Left
5	Mongrel dog	M	28	8	hip dislocation and mild bilateral coxarthrosis	Left
6	Schnauzer mix	C	13.5	8	hip dislocation and moderate bilateral coxarthrosis	Right
7	Hunting dog	C	29	54	severe coxarthrosis on left side	Left
8	Bernese mountain dog	M	39.5	22	severe bilateral coxarthrosis	Right
9	Bernese mountain dog	M	36.7	12	hip dislocation and mild bilateral coxarthrosis	Left
10	Pekinese	C	5.6	67	femoral head defect left side (Legg Calve Perthes disease)	Left
11	German shepherd	C	33.3	91	severe bilateral coxarthrosis	Right
12	German shepherd mix	C	24.6	19	severe coxarthrosis on right side	Right
13	Labrador	M	34	50	severe coxarthrosis on left side	Left
14	Schanuzer mix	M	40	79	severe coxarthrosis on right side, mild coxarthrosis on left side	Right
15	Mongrel dog	M	50.7	148	severe bilateral coxarthrosis	Right
16	Labrador	C	34.5	102	severe bilateral coxarthrosis	Left
17	Labrador	C	23.6	90	severe bilateral coxarthrosis	Left
18	Golden retriever	M	30.5	138	severe bilateral coxarthrosis	Right
19	Bernese mountain dog	C	60.5	81	severe bilateral coxarthrosis	Right
20	German shepherd Mix	C	37.5	Unknown	severe bilateral coxarthrosis	Left
21	Dobermann	C	26.6	120	severe bilateral coxarthrosis	Left
22	Labrador	C	26	50	severe bilateral coxarthrosis	Left

23	German shepherd	C	37	36	severe bilateral coxarthrosis	Right
24	Mongrel dog	M	20	115	severe bilateral coxarthrosis	Left
25	German shepherd	C	37.5	58	severe coxarthrosis on right side, hip prosthesis leftside	Right
26	German shepherd	C	41.2	98	severe bilateral coxarthrosis	Left
27	Golden retriever	C	47.7	96	severe bilateral coxarthrosis	Right
28	Labrador mix	C	30.6	47	severe bilateral coxarthrosis	Right
29	Labrador mix	C	34	108	severe coxarthrosis on left side, hip prosthesis on right side	Left
30	Mongrel dog	M	36	79	severe bilateral coxarthrosis	Right
31	Old german shepherd	M	33.4	97	severe coxarthrosis on left side, mild coxarthrosis on right side	Left
32	Rhodesian ridgeback	M	36.5	8	hip subluxation and atrophy of the neck on left side	Left
33	Golden retriever	M	33	8	hip dislocation both sides, mild bilateral coxarthrosis	Left
34	Irish setter	M	45.5	84	severe bilateral coxarthrosis	Left
35	Airdale terrier	C	25	96	severe coxarthrosis on left side, mild coxarthrosis on right side	Left
36	German shepherd mix	M	28	36	hip dislocation both sides, moderate bilateral coxarthrosis	Left
37	Mongrel dog	C	32.7	15	moderate coxarthrosis on right side, hip prosthesis on left side	Right
38	Mongrel dog	M	20.5	11	Bilateral hip dislocation, mild bilateral coxarthrosis	Left
39	Comondor	C	43.8	Unknown	moderate coxarthrosis on left side, mild coxarthrosis on right side	Left

Table 3: Average body weight, age, anaesthesia time, surgery time and amount of intraoperative fentanyl in both groups

Group	Weight (kg) ± SD	Age (years) ± SD	Anaesthesia time (min) ± SD	Surgery time (min) ± SD	Intraoperative fentanyl (µg/kg/h) ± SD
M	33.59 ± 7.34	4.74 ± 3.93	276.67 ± 25.95	97.68 ± 9.79	9.77 ± 2.93
C	32.21 ± 11.56	5.62 ± 2.77	286.47 ± 22.83	97.45 ± 12.25	11.67 ± 3.92

None of the patients presented a surgical complication. All animals woke up from the anaesthesia without major adverse reactions. During the stay in the hospital six patients (15.4%) presented diarrhoea. Five of them belonged to group M and only one to group C. Three patients belonging to the group M (7.7%) vomited during the course of the study. One of them developed excessive vomiting and the metamizole therapy was discontinued. This patient was immediately excluded from the study and the following evaluations.

1. Pain scores

All dogs could be subjectively evaluated with both pain scoring systems (mMPS and VAS) except for one patient that became aggressive despite the administration of rescue analgesia. Due to his temper evaluations could not be performed after T_{25}.

1.1. Rescue analgesia

Out of the 39 patients evaluated, three needed rescue analgesia (10 µg·kg^{-1} buprenorphine IV) (table 4 and 5) and were subsequently excluded from the statistical analysis and did not participate in the gait analysis. All of these patients were in group C. One of them scored 61 points for VAS and 19 points for mMPS immediately after extubation. The dog quickly received the rescue analgesia and by the next evaluation (T_0) the scores had decreased to 41 for VAS and to 10 for mMPS (data not shown). The other two dogs woke up without problems, but by the first evaluation (T_0) they scored 50 and 74 points for VAS and 14 points for mMPS. The patient who showed 74 points for the VAS did not respond well to the initial therapy with 10 µg·kg^{-1} buprenorphine and hence the same dose of buprenorphine was repeated for a second time. The following assessment (T_3) still revealed a VAS score greater than 50 and it was decided to administer metamizole

(50 mg·kg^{-1}) IV. Because the study was blinded, the evaluator (AS) did not know that this time metamizole and not buprenorphine was administered. The scores at the following evaluation (T_6) had decreased to10 points for mMPS, but remained at 50 points for VAS. From T_{25} on it was impossible to conduct any further pain evaluation because the dog was too aggressive. The patient continued on buprenorphine (10 µg·kg^{-1} TID) and metamizole (50 mg·kg^{-1} TID). The last dog that received rescue analgesia responded very well to the therapy: at T_3 VAS and mMPS scores went down from 50 to 26 points and from 14 to 4 points, respectively (figure 9 and 10).

Table 4: mMPS scores rescue analgesia. mMPS = modified Melbourne Pain Scale; ID = identification number; * = pain evaluation immediately after extubation; ** = impossible to evaluate because of aggression.

ID	T0	T3	T6	T9	T17	T21	T25	T29	T33	T41	T45	T53
100637	14	12	10	10	9	8	**					
100699	14	4	8	7	6	4	2	3	3	3	2	1
101989	19*	9	11	6	8	4	4	4	4	3	4	2

Table 5: VAS scores rescue analgesia. VAS = visual analogue scale; ID = identification number; * = pain evaluation immediately after extubation; ** = impossible to evaluate because of aggression

ID	T0	T3	T6	T9	T17	T21	T25	T29	T33	T41	T45	T53
100637	74	58	52	50	50	45	**					
100699	50	26	43	39	34	32	15	27	25	25	22	14
101989	61*	41	50	30	31	29	24	25	25	20	21	20

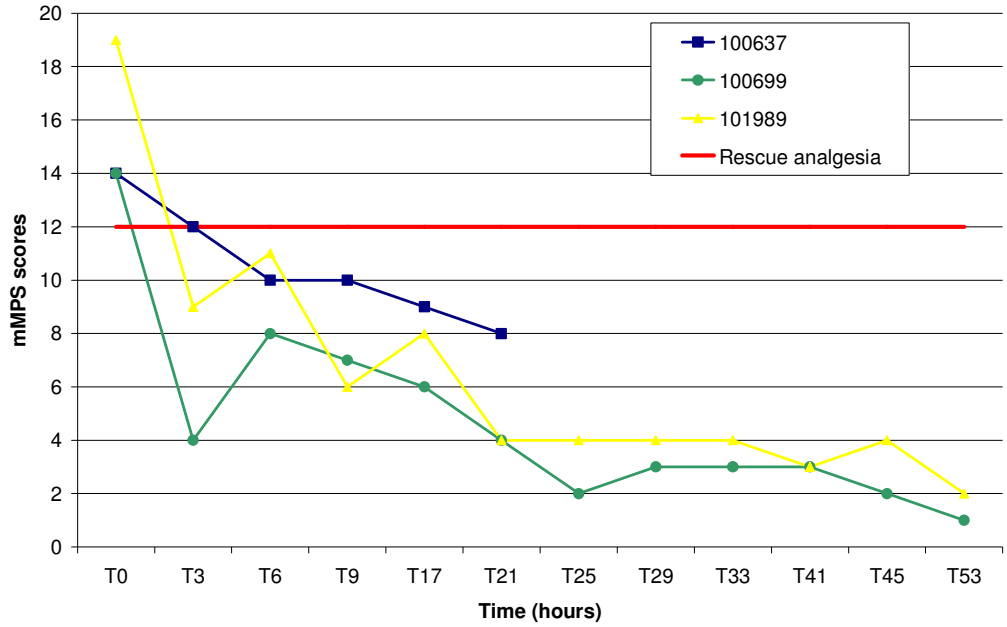

Figure 9: mMPS score before and after rescue analgesia.

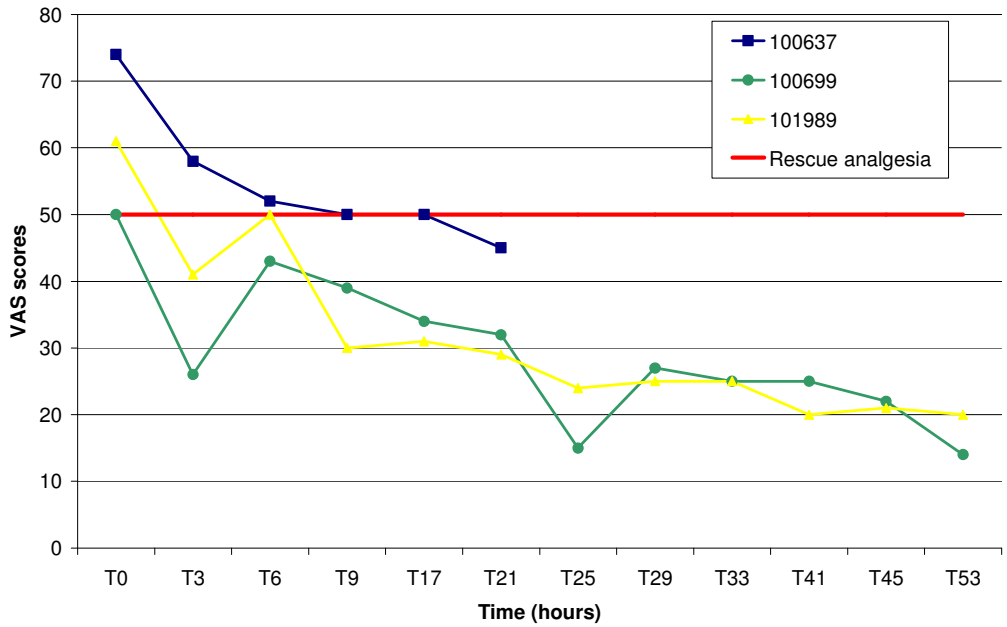

Figure 10: VAS score before and after rescue analgesia.

1.2. Modified Melbourne pain score (mMPS)

The results of the mMPS assessments are shown in table 6 and 7.

Table 6: mMPS scores and mean values over the time for dogs in group M. SD = standard deviation; ** = patient excluded because of excessive vomiting; * = patient went home

ID	T0	T3	T6	T9	T17	T21	T25	T29	T33	T41	T45	T53
100400	4	4	4	3	4	4	2	1	0	1	0	1
96614	4	5	7	4	2	2	2	2	2	2	3	1
98905	5	5	6	6	3	5	7	4	4	4	3	3
99749	9	4	3	3	4	3	3	1	3	5	2	0
101107	6	5	4	6	6	5	3	5	3	4	2	2
95791	6	9	8	4	3	3	3	4	3	1	3	3
102408	8	6	5	4	4	4	2	2	5	1	2	1
101516	8	9	5	4	7	3	3	4	4	1	3	2
101313	5	5	5	3	3	4	2	1	1	0	1	1
101656	4	3	6	2	5	4	3	2	1	1	0	*
101886	7	6	5	4	3	3	3	2	1	2	2	0
101872	7	9	9	9	9	7	4	4	2	4	1	1
99283	8	4	6	8	6	3	1	1	0	2	1	1
103480	11	3	5	4	2	3	0	0	1	2	1	0
103521	9	9	9	6	9	7	7	5	4	3	3	2
103369	5	4	5	6	3	2	1	0	0	1	0	0
96051	5	5	3	2	2	4	**					
100842	4	4	4	4	3	4	1	0	0	2	2	0
102611	9	8	7	5	5	6	5	5	5	3	3	*
Mean ± SD	**6.63 ± 2.09**	**5.69 ± 2.12**	**5.63 ± 1.78**	**4.88 ± 1.78**	**4.44 ± 2.27**	**3.88 ± 1.5**	**2.75 ± 1.94**	**2.25 ± 1.8**	**2.06 ± 1.69**	**2.19 ± 1.42**	**1.81 ± 1.04**	**1.13 ± 1.02**

Table 7: mMPS scores over time for dogs in group C. SD = standard deviation; * = patient went home.

ID	T0	T3	T6	T9	T17	T21	T25	T29	T33	T41	T45	T53
100880	9	7	8	8	7	7	6	6	6	6	7	8
100698	9	8	9	6	11	6	10	5	4	5	11	9
101487	5	6	6	8	7	6	5	5	2	3	5	3
101488	6	6	6	6	4	6	6	5	3	3	6	5
101841	10	9	6	10	6	7	3	3	4	4	5	3
95904	8	10	10	10	8	6	6	4	5	3	4	2
102431	7	7	6	5	3	7	3	2	1	4	0	0
101975	4	7	10	9	8	6	5	3	5	2	2	2
102086	8	8	7	5	5	2	2	1	4	0	0	0
102347	9	5	8	8	11	3	8	5	3	5	3	2
96359	5	4	0	2	0	0	3	0	0	0	3	0
102404	7	6	4	5	5	4	2	2	2	1	1	2
102628	11	6	4	5	5	5	5	2	2	5	3	1
94614	5	7	6	9	8	6	4	3	4	4	3	1
91538	6	5	7	7	7	7	4	5	6	5	3	3
101107	7	6	3	3	7	8	6	7	8	4	6	6
103969	9	8	6	4	3	6	4	4	4	4	2	*
Mean ± SD	**7.25 ± 2.02**	**6.69 ± 1.54**	**6.25 ± 2.62**	**6.63 ± 2.39**	**6.38 ± 2.78**	**5.38 ± 2.13**	**4.88 + 2.16**	**3.63 ± 1.93**	**3.69 ± 2.06**	**3.38 ± 1.82**	**3.88 ± 2.8**	**2.94 ± 2.74**

Except for the three dogs that received rescue analgesia mMPS scores revealed good pain relief for both groups during the entire evaluation period (pain score < 12). At T_0, scores in both groups were over 6 points and no statistical differences were found ($p = 0.21$). At the next evaluation (T_3), scores of dogs in group M had decreased to 5.69 ± 2.12. Scores of dogs in group C remained over 6 points (6.69 ± 1.54) and did not decrease until T_{21} (5.38 ± 2.13). A significant difference between the groups was found at T_3 ($p = 0.04$) and between T_9 and the end of the study ($p < 0.05$). Dogs in the group M showed lower mMPS scores during the whole study (table 8, figure 11).

Table 8: mMPS mean values for dogs in group M and C. SD = standard deviation; p = significance level ≤ 0.05.

Evaluation time	Group M	Group C	Mann Whitney Test
	Mean + SD	Mean + SD	P
T_0	6.63 ± 2.09	7.25 ± 2.02	0.21
T_3	5.69 ± 2.12	6.69 ± 1.54	**0.04**
T_6	5.63 ± 1.78	6.25 ± 2.62	0.19
T_9	4.88 ± 1.78	6.63 ± 2.39	**0.02**
T_{17}	4.44 ± 2.28	6.38 ± 2.78	**0.02**
T_{21}	3.88 ± 1.50	5.38 ± 2.13	**0.01**
T_{25}	2.75 ± 1.95	4.88 ± 2.16	**0.01**
T_{29}	2.25 ± 1.80	3.63 ± 1.93	**0.05**
T_{33}	2.06 ± 1.69	3.69 ± 2.06	**0.03**
T_{41}	2.19 ± 1.42	3.38 ± 1.82	**0.03**
T_{45}	1.81 ± 1.05	3.88 ± 2.80	**0.01**
T_{53}	1.13 ± 1.03	2.94 ± 2.74	**0.04**

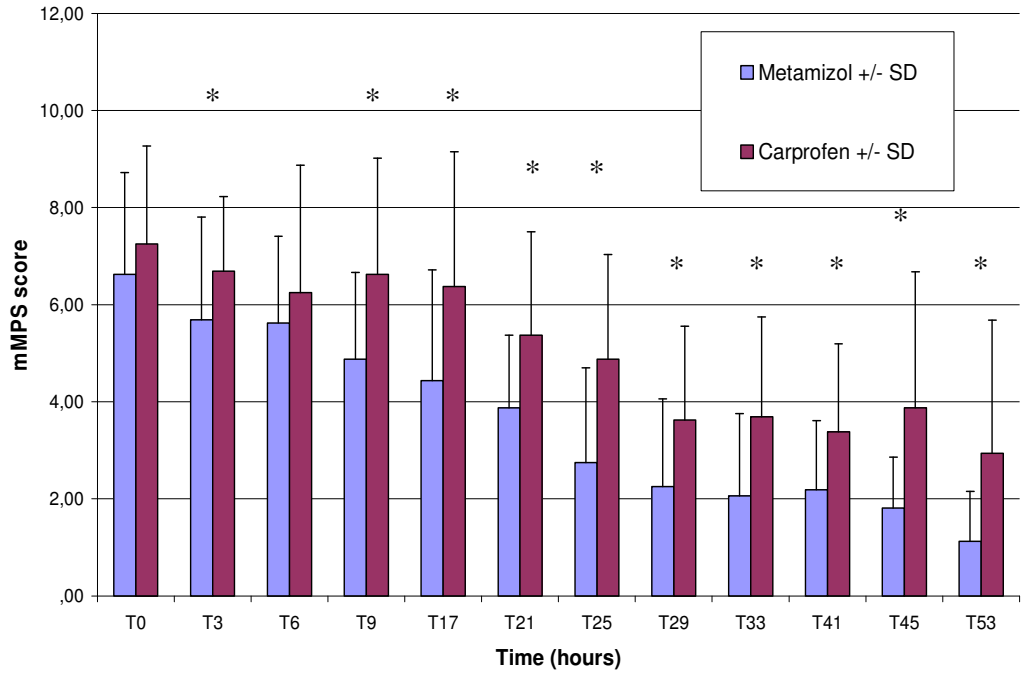

Figure 11: mMPS score over time for dogs in the group M and C.

*** = statistically significant differences (p ≤ 0.05).**

1.3. Visual analogue scale (VAS)

The results of the VAS scores are shown in table 9 and 10.

Table 9: VAS scores over time for dogs in group M. SD = standard deviation; ** = patient excluded because of excessive vomiting; * = patient went home

ID	T0	T3	T6	T9	T17	T21	T25	T29	T33	T41	T45	T53
100400	33	31	26	28	22	23	25	14	17	11	9	5
96614	42	40	37	40	29	24	19	12	18	13	13	6
98905	31	33	35	43	38	38	37	27	29	27	25	21
99749	39	40	27	30	29	25	26	20	19	23	19	17
101107	39	43	30	34	35	30	30	26	24	26	17	17
95791	37	41	41	37	35	31	33	34	30	24	28	26
102408	46	41	37	33	29	27	29	23	25	25	23	20
101516	43	47	32	30	27	27	28	27	27	22	20	22
101313	26	25	29	21	23	20	13	8	9	5	6	5
101656	20	27	27	25	19	28	22	20	15	12	11	*
101886	32	35	29	31	31	25	24	24	22	22	20	11
101872	41	39	42	39	43	29	27	23	23	27	15	15
99283	33	29	32	31	31	15	14	11	0	8	0	0
103480	39	31	22	22	17	18	10	7	5	8	7	0
103521	32	32	35	24	32	22	24	20	20	21	14	12
103369	21	16	17	17	13	11	6	0	0	0	0	0
96051	25	21	19	19	15	20	**					
100842	27	26	26	20	20	25	10	6	5	4	8	0
102611	44	42	39	34	30	35	27	25	20	23	20	*
Mean ± SD	**34.21 ± 7.81**	**33.63 ± 8.31**	**30.63 ± 7.07**	**29.37 ± 7.58**	**27.26 ± 8.08**	**24.89 ± 6.55**	**22.44 ± 8.65**	**18.17 ± 9.13**	**17.11 ± 9.53**	**16.72 ± 8.98**	**14.17 ± 8.1**	**11.25 ± 8.93**

Table 10: VAS score over time for dogs in group C. SD = standard deviation; * = Patient went home

ID	T0	T3	T6	T9	T17	T21	T25	T29	T33	T41	T45	T53
100880	46	44	44	49	37	34	32	31	31	31	32	39
100698	45	46	44	39	43	39	43	45	40	39	33	44
101487	40	37	41	44	35	37	33	32	29	29	44	31
101488	42	43	42	46	42	46	40	30	30	29	36	29
101841	43	39	38	35	35	39	36	30	26	28	27	26
95904	40	43	43	43	35	40	30	30	32	29	29	19
102431	31	32	25	24	21	24	16	14	16	10	11	5
101975	11	23	46	31	30	27	25	24	24	16	12	8
102086	31	32	31	28	24	19	16	15	21	7	0	0
102347	36	27	30	32	29	24	26	28	29	28	25	20
96359	28	22	23	23	11	6	14	9	0	0	12	0
102404	32	29	23	26	19	17	14	17	15	12	13	12
102628	46	30	27	25	33	29	28	19	19	24	19	7
94614	31	43	39	39	43	32	25	17	21	23	20	13
91538	42	40	42	40	42	34	32	28	30	31	24	19
101107	39	36	30	30	32	36	34	31	29	26	28	28
103969	39	32	33	25	27	29	20	23	27	23	17	*
Mean ± SD	**36.59 ± 8.75**	**35.18 ± 7.52**	**35.35 ± 8.01**	**34.06 ± 8.47**	**31.65 ± 9.1**	**30.17 ± 9.96**	**27.29 ± 8.97**	**24.88 ± 8.87**	**24.65 ± 8.96**	**22.65 ± 10.23**	**22.47 ± 11.02**	**18.75 ± 13.33**

Except for the three dogs that received rescue analgesia VAS scores revealed good pain relief for both groups during the entire evaluation period (VAS score < 50). From T_0 to T_{17} both groups scored quiet similar and no statistical differences were found until T_{21} ($p = 0.05$). Except for T_{25} ($p = 0.11$) and T_{53} ($p = 0.11$) the following evaluations showed significant differences, too ($p \leq 0.05$). Group M showed lower VAS scores during the whole study period (table 11, figure 12).

Table 11: VAS mean values for dogs in group M and C. SD = standard deviation; p = significance level ≤ 0.05.

Evaluation period	Group M	Group C	Man Whitney Test
	Mean + SD	Mean + SD	P
T0	35.06 ± 6.86	36.44 ± 9.02	0.30
T3	34.31 ± 8.01	35.38 ± 7.72	0.46
T6	31.06 ± 6.73	35.5 ± 8.25	0.07
T9	30 ± 7.67	34.63 ± 8.41	0.12
T17	28.38 ± 7.87	31.94 ± 9.32	0.11
T21	24.38 ± 6.49	30.19 ± 10.29	**0.05**
T25	22.19 ± 9.13	27.75 ± 9.06	0.11
T29	17.63 ± 9.54	25 ± 9.15	**0.04**
T33	17.06 ± 10.1	24.5 ± 9.24	**0.02**
T41	16.63 ± 9.34	22.63 ± 10.56	**0.03**
T45	14 ± 8.45	22.81 ± 11.29	**0.02**
T53	11.06 ± 8.93	18.75 ± 13.33	0.09

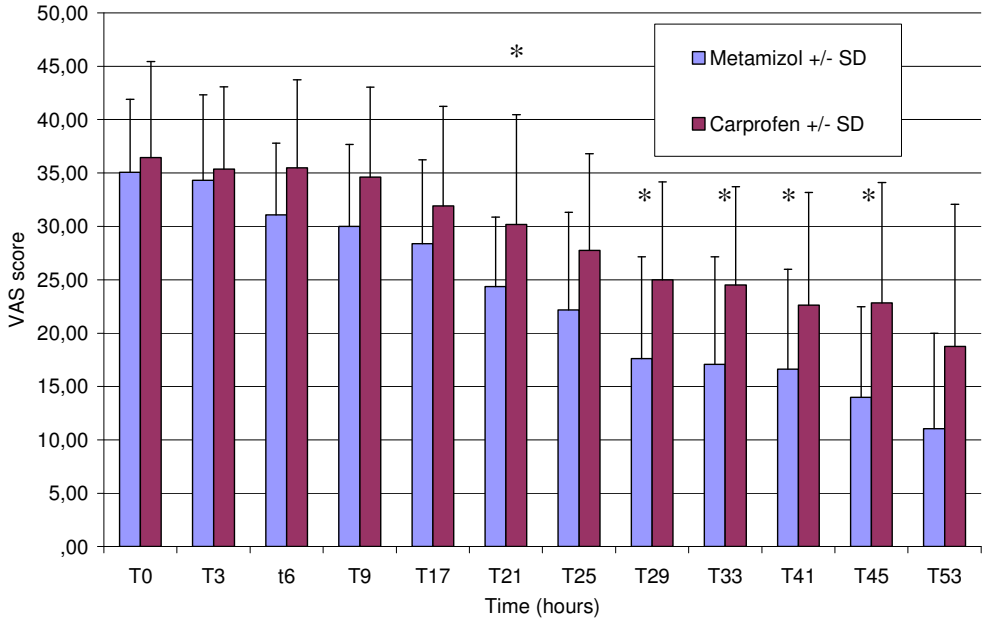

Figure 12: VAS score over time for dogs in the group M and C.

*** = statistically significant differences (p ≤ 0.05).**

2. Ground reaction forces (GRF)

Force plate analysis was performed in thirty-four patients (94.4%). Only one dog in group C did not tolerate the examination for unknown reasons and one dog in group M was a measurement error. The examination was possible in eighteen dogs of group M (94.7%) and sixteen dogs of group C (94.1 %). During the preoperative gait analysis dogs in group C and M walked at a speed of 0.62 $\pm$ 0.06 m/s and 0.67 $\pm$ 0.1 m/s, respectively. As expected, the speed of the treadmill had to be slowed down for the postoperative examinations. On the first and second postoperative days the speed for animals in group C was decreased to 0.05 $\pm$ 0.03 m/s and 0.03 $\pm$ 0.03 m/s, respectively. For dogs in group M it was decreased to 0.04 $\pm$ 0.05 m/s and 0.03 $\pm$ 0.05 m/s on the first and second postoperative days, respectively. This reduction in speed was significant in both groups, but between groups no statistical speed differences were found.

Except for three dogs in group M all patients tolerated the examinations well. Of these three dogs, one refused to walk on the treadmill on the first postoperative day and two refused to walk on the treadmill on the second postoperative day.

2.1. Peak vertical force

The peak vertical force (PVF) of the hind limbs were measured and expressed in percentage of body weight (%BW). Then a relation between the values obtained for the operated hind limb and the contralateral non operated hind limb was calculated and expressed as a percentage (op/nop%). Data are shown in tables 12 and 13.

Table 12: Peak vertical force (%BW) of dogs in the group M. preOP = preoperative day; OP1 = first postoperative day; OP2 = second postoperative day. Op = operated hind limb; nop = non operated hind limb; * = patient refuse to walk.

	preOP			OP1			OP2		
ID	Op	nop	**op/nop%**	op	nop	**op/nop%**	Op	nop	**Op/nop%**
95791	35.8	35.9	**99.72**	32.6	36.5	**89.32**	31.2	34.2	**91.23**
98095	38.8	35.3	**109.92**	34.3	39.4	**87.06**	36.4	41.7	**87.29**
96051	39.0	38.2	**102.09**	36.1	42.3	**85.34**	*	*	
99283	34.0	36.3	**93.66**	36.0	40.6	**88.67**	32.4	36.0	**90.00**
99749	36.6	41.0	**89.27**	37.0	44.4	**83.33**	36.0	40.7	**88.45**
100400	34.9	35.6	**98.03**	*	*		34.8	36.9	**94.31**
100842	35.2	34.1	**103.23**	36.1	40.8	**88.48**	36.6	38.7	**94.57**
101107	30.5	33.9	**89.97**	28.0	31.9	**87.77**	34.4	34.6	**99.42**
101313	36.7	39.5	**92.91**	37.5	38.5	**97.40**	34.0	36.8	**92.39**
101408	37.6	36.8	**102.17**	35.0	34.5	**101.45**	33.6	35.8	**93.85**
101516	35.5	35.1	**101.14**	31.0	34.8	**89.08**	32.9	34.3	**95.92**
101656	33.7	35.4	**95.20**	29.6	35.7	**82.91**	31.5	36.4	**86.54**
101872	35.4	38.4	**92.19**	33.5	38.6	**86.79**	41.4	45.4	**91.19**
101886	36.6	39.9	**91.73**	36.0	40.0	**90.00**	37.1	39.4	**94.16**
102611	34.5	37.3	**92.49**	33.0	36.6	**90.16**	36.7	44.6	**82.29**
103369	36.0	37.2	**96.77**	34.0	34.9	**97.42**	38.9	41.6	**93.51**
103480	37.4	37.6	**99.47**	34.3	40.9	**83.86**	*	*	
103521	37.1	37.5	**98.93**	33.9	40.2	**84.33**	34.4	41.9	**82.10**
Mean ± SD			**97.16 ± 5.45**			**89.02 ± 5.25**			**91.08 ± 4.77**

Table 13: Peak vertical force (%BW) for dogs in the group C. preOP = preoperative day; OP1 = first postoperative day; OP2 = second postoperative day. Op = operated hind limb; nop = non operated hind limb.

	preOP			OP1			OP2		
ID	Op	Nop	**op/nop%**	Op	nop	**op/nop%**	op	nop	**Op/nop %**
94614	37.9	38.0	**99.7**	34.5	37.4	**92.25**	36.1	37.6	**96.01**
100698	34.4	35.0	**98.3**	26.7	43.6	**61.24**	24.9	45.0	**55.33**
96359	32.7	33.9	**96.5**	31.0	37.0	**83.78**	31.1	34.9	**89.11**
101107	39.8	40.5	**98.3**	29.8	42.6	**69.95**	37.6	53.2	**70.68**
101487	37.7	37.8	**99.7**	33.1	33.9	**97.64**	34.0	36.4	**93.41**
101488	49.7	52.7	**94.3**	48.0	54.3	**88.40**	49.0	52.6	**93.16**
101841	30.3	38.5	**78.7**	27.6	38.8	**71.13**	30.1	38.8	**77.58**
101975	32.3	34.5	**93.6**	34.4	37.3	**92.23**	36.6	39.2	**93.37**
102086	30.4	36.0	**84.4**	34.0	40.6	**83.74**	31.1	35.2	**88.35**
102347	37.2	37.7	**98.7**	35.4	39.3	**90.08**	29.4	37.8	**77.78**
102404	39.6	38.8	**102.1**	35.5	39.0	**91.03**	37.9	40.7	**93.12**
102431	34.8	34.6	**100.6**	32.9	37.7	**87.27**	32.0	34.8	**91.95**
103969	36.2	50.2	**72.1**	38.4	46.6	**82.40**	36.9	47.9	**77.04**
102628	36.6	36.4	**100.5**	35.3	40.4	**87.38**	35.7	39.8	**89.70**
91538	35.5	35.9	**98.9**	30.1	51.6	**58.33**	32.9	46.1	**71.37**
95904	35.9	36.6	**98.1**	31.2	39.1	**79.80**	32.7	35.9	**91.09**
Mean ± SD			**94.66 ± 8.64**			**82.29 ± 11.44**			**84.31 ± 11.44**

Analyzing the data one can appreciate that the relation of the PVF of the operated limb to the non operated limb was similar before surgery between groups ($p = 0.31$). On the first postoperative day the PVF of the operated leg decreased significantly compared to the non operated limb in both groups ($p = 0.001$ for both groups). On the second postoperative day a tendency of the calculated ratio to return to its preoperative value could be observed, but in both groups the ratio was still significantly lower than during the preoperative evaluation ($p = 0.004$ for both groups). However, the PVF ratio for dogs in group M was significantly higher than in group C on both postoperative days ($p = 0.04$) (figure 13, table 14).

Table 14: Mean values of PVF for dogs in the groups M and C.

SD = standard deviation; p = significance level < 0.05

Day of examination	Group M Mean ± SD	Group C Mean ± SD	T test P
preOP	97.16 ± 5.45	94.66 ± 8.64	0.31
OP1	89.02 ± 5.25	82.29 ± 11.44	**0.04**
OP2	91.08 ± 4.77	84.31 ± 11.44	**0.04**

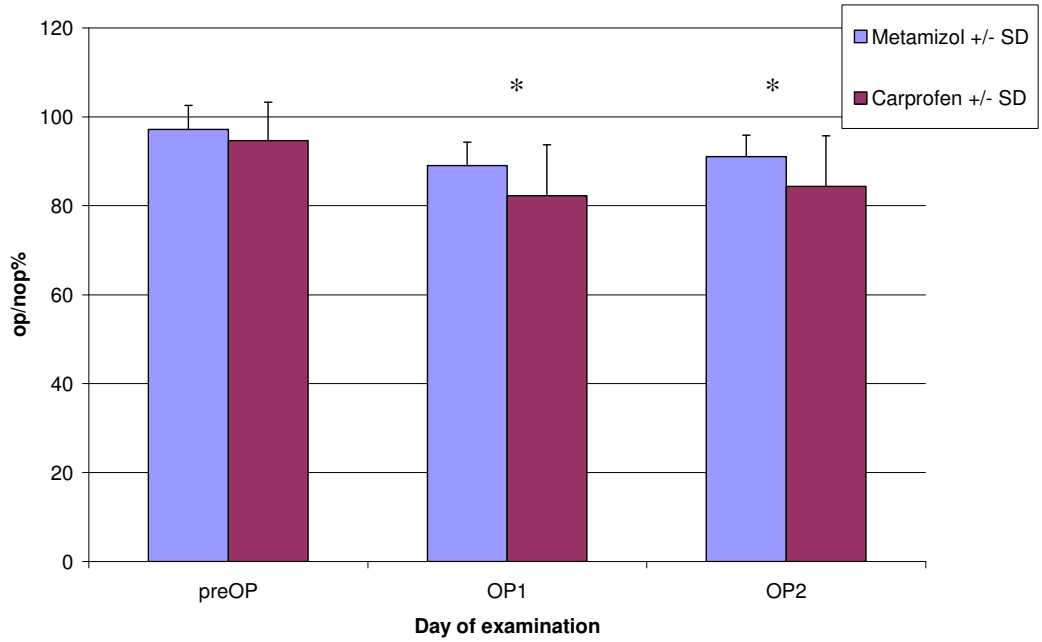

Figure 13: Peak vertical force ratio (op/nop%) of dogs in the groups M and C.

*** = statistically significant differences (p ≤ 0.05).**

2.2. Vertical impulse

The vertical impulse (VI) of the hind limbs was measured and expressed in Newton per second (Ns). A relation between the values obtained for the operated hind limb and the non operated hind limb was calculated and expressed as a percentage (op/nop%). Data are shown in table 15 and16,

Table 15: Vertical impulse (Ns) for dogs in the group M. preOP = preoperative day; OP1 = first postoperative day; OP2 = second postoperative day; op = operated hind limb; nop = non operated hind limb; * = patient refuse to walk.

	preOP			OP1			OP2		
ID	**op**	**Nop**	**op/nop%**	**Op**	**nop**	**op/nop%**	**Op**	**nop**	**op/nop%**
95791	0.15	0.16	**99.35**	0.14	0.15	**92.00**	0.14	0.15	**90.67**
98095	0.14	0.14	**100.71**	0.12	0.16	**76.43**	0.12	0.16	**75.16**
96051	0.14	0.14	**102.19**	0.12	0.15	**82.00**	*	*	
99283	0.11	0.13	**79.55**	0.09	0.13	**70.45**	0.10	0.13	**79.37**
99749	0.12	0.15	**77.27**	0.11	0.16	**68.55**	0.09	0.16	**53.75**
100400	0.11	0.15	**71.24**	*	*		0.12	0.14	**81.25**
100842	0.12	0.13	**92.80**	0.11	0.15	**74.48**	0.11	0.13	**86.15**
101107	0.08	0.09	**88.04**	0.09	0.11	**76.99**	0.13	0.12	**111.02**
101313	0.14	0.17	**83.83**	0.13	0.16	**81.65**	0.12	0.14	**87.32**
101408	0.14	0.15	**91.95**	0.11	0.12	**89.43**	0.12	0.13	**90.23**
101516	0.15	0.15	**99.34**	0.11	0.13	**86.05**	0.14	0.13	**100.75**
101656	0.16	0.19	**81.44**	0.13	0.20	**62.87**	0.14	0.21	**67.63**
101872	0.14	0.14	**93.75**	0.11	0.15	**73.15**	0.14	0.16	**85.44**
101886	0.11	0.17	**67.07**	0.11	0.14	**74.47**	0.11	0.14	**74.13**
102611	0.08	0.08	**96.25**	0.05	0.07	**75.71**	0.05	0.08	**58.02**
103369	0.12	0.11	**103.60**	0.10	0.12	**82.91**	0.13	0.12	**100.81**
103480	0.13	0.13	**99.24**	0.11	0.16	**69,.81**	*	*	
103521	0.16	0.15	**102.63**	0.15	0.22	**66.97**	0.13	0,19	**68.39**
Mean + SD			**90.57 + 11.35**			**76.7 + 8.05**			**81.88 + 15.55**

Table 16: Vertical impulse (Ns) for the dogs in the group C. preOP = preoperative day; OP1 = first postoperative day; OP2 = second postoperative day. Op = operated hind limb; nop = none operated hind limb.

	preOP			OP1			OP2		
ID	**op**	**Nop**	**op/nop%**	**Op**	**nop**	**op/nop%**	**Op**	**nop**	**op/nop%**
94614	0.13	0.16	**80.25**	0.11	0.15	**72.11**	0.11	0.13	**81.20**
100698	0.12	0.15	**76.16**	0.06	0.19	**32.29**	0.06	0.20	**28.06**
96359	0.15	0.18	**81.42**	0.11	0.23	**48.67**	0.12	0.21	**58.22**
101107	0.11	0.14	**80.71**	0.07	0.12	**59.84**	0.10	0.17	**58.33**
101487	0.17	0.20	**86.80**	0.13	0.18	**72.16**	0.13	0.17	**75.44**
101488	0.17	0.22	**78.90**	0.17	0.22	**77.03**	0.16	0.24	**66.80**
101841	0.13	0.17	**76.02**	0.07	0.16	**47.74**	0.08	0.18	**46.15**
101975	0.13	0.14	**92.20**	0.15	0.21	**72.68**	0.15	0.16	**97.45**
102086	0.09	0.11	**84.68**	0.12	0.14	**89.78**	0.11	0.11	**94.59**
102347	0.16	0.18	**87.64**	0.13	0.19	**68.75**	0.12	0.26	**45.74**
102404	0.15	0.15	**97.40**	0.15	0.17	**92.17**	0.15	0.15	**98.04**
102431	0.13	0.15	**85.71**	0.12	0.17	**74.25**	0.11	0.16	**69.14**
103969	0.13	0.17	**75.30**	0.14	0.18	**79.21**	0.11	0.15	**77.93**
102628	0.12	0.12	**101.68**	0.10	0.12	**83.74**	0.10	0.13	**76.12**
91538	0.09	0.10	**92.16**	0.05	0.10	**47.96**	0.06	0.10	**58.16**
95904	0.12	0.14	**81.12**	0.09	0.17	**50.29**	0.10	0.17	**59.39**
Mean ± SD			**84.89 ± 7.77**			**66.79 ± 17.18**			**68.17 ± 19.67**

Observing the data one can appreciate that the relation of the VI of the operated limb to the non-operated limb (op/nop%) before surgery was similar between groups ($p = 0.1$). On the first postoperative day the VI of the operated limb in both groups decreased significantly in relation to the non operated limb ($p < 0.001$ in group C and $p = 0.02$ in group M). On the second postoperative day VI values in group C showed a tendency to return to preoperative values, but were still significantly lower than preoperative values ($p = 0.002$). On the other side, VI values of dogs in group M showed no statistical differences on the second postoperative day compared to preoperative values ($p = 0.09$). Furthermore, the decrease of the vertical impulse for dogs in group M was lesser compared to that of dogs in group C on both postoperative days ($p = 0.04$) (figure 14, table 17).

Table 17: Mean values of the VI of dogs in the groups M and C. SD = standard deviation; p = significance level < 0.05

Day of examination	Group M	Group C	T test
	Mean + SD	Mean + SD	P
preOP	90.57 + 11.35	84.89 ± 7.77	0.1
OP1	76.7 + 8.05	66.79 ± 17.18	**0.04**
OP2	81.88 + 15.55	68.17 ± 19.67	**0.04**

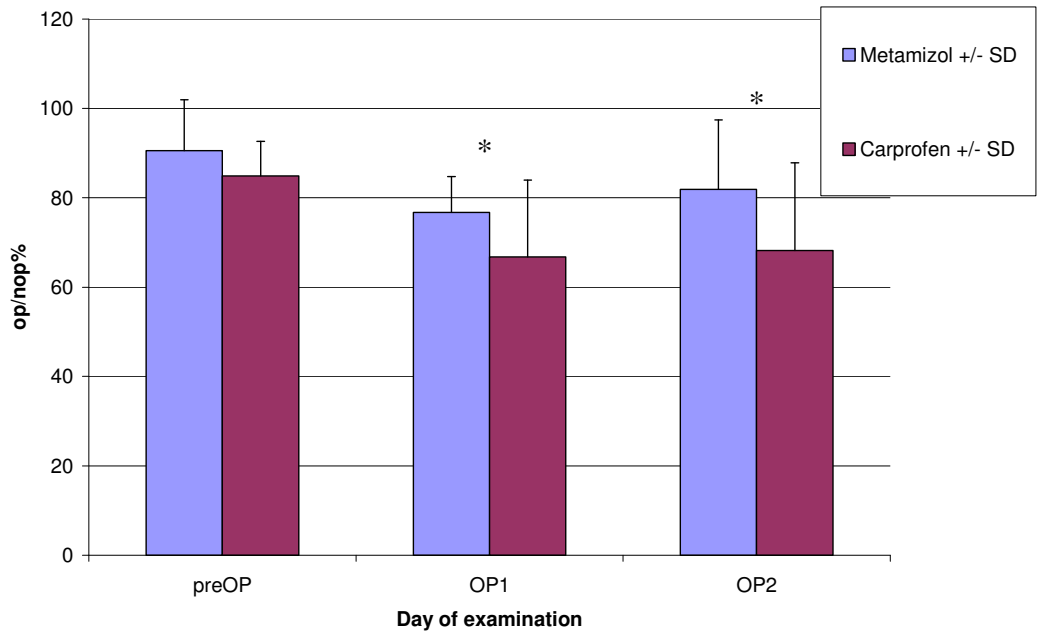

Figure 14: Vertical impulse ratio (op/nop%) of dogs in the groups M and C.

*** = statistical differences (p ≤ 0.05).**

VI. DISCUSSION

Total hip replacement in dogs is a procedure that requires intraoperative pain management (RICHTER, 2007) and in spite of the surgeon's care, tissue damage and cell destruction with the consequent liberation of inflammatory mediators of pain occurs (DRAY, 1995; LASCELLES et al., 1997). Increased knowledge, changing attitudes, and greater sensibility for animal welfare have increased the desire to treat pain in veterinary practice (MUIR et al., 2001). Additionally, an appropriate post-operative pain therapy with few or even no side effects has proven to result in a better and more satisfactory recovery (KEHLET and DAHL, 1993). A lot of analgesic techniques have been applied both in humans as well as in veterinary medicine after orthopaedic surgery: those that include NSAIDS or opioids as sole analgesics and others that use a combination of several drugs to achieve superior pain relief (SINGELYN and GOUVERNNEUR, 1999; LAREDO et al., 2004; REMÉRAND et al., 2009). We decided to perform the study in dogs receiving a total hip replacement because this surgery is a well standardized procedure at our institution. Additionally, before the start of this research project we had the subjective impression that the sole use of a classical NSAID (e.g. carprofen) following THR in dogs often may not lead to sufficient analgesia. Therefore our aim was to find out whether postoperative analgesia might be superior with the use of metamizole. We decided to investigate the analgesic efficacy of sodium metamizole because of its recognized potency in human medicine and its few adverse effects compared to opioids (TORRES et al., 2001; STRAMER et al., 2003). We compared metamizole's efficacy with carprofen a recognized NSAID in veterinary medicine. Carprofen has demonstrated good pain relief after various types of surgeries in several clinical studies (NOLAN and REID, 1993; LASCELLES et al., 1994; LASCELLES et al., 1998; GRISNEAUX et al., 1999; LAREDO et al., 2004; LEECE et al., 2005). All dogs were operated by the same surgeon and except for the postoperative analgesic regimen followed the same postoperative care. Based on the author's knowledge, there are no studies on the clinical efficacy of metamizole after surgery in dogs.

Mechanisms of pain have been profoundly studied, yet there is still an incomplete understanding of all the processes that finally lead to the conscious perception of

pain. A lot of anatomical structures and biochemical components participate and influence the four stages of nociception: transduction, transmission, modulation and perception (LAMONT, 2000; LEMKE, 2004). Therefore, the possibility that only one agent can completely block nociception is improbable. Due to this, it is common practice to combine different analgesics, and this approach has increased significantly over the last decade (ILKIW, 1999; GONZÁLEZ de MEJÍA, 2005; HELLYER, 2007). The complexity of pain physiology and thus the difficulty to standardize animals' pain models makes experimental and clinical studies of different drugs very difficult and often leads to contradicting results (LAMONT, 2000; LeBARS et al., 2001). In other words each species reacts differently to different stimuli and furthermore a psychological component may also be present (DEGENAAR 1979). Another factor that surely plays an important role is pain assessment. In clinical studies in humans the verbal expression of perceived pain allows a more reliable evaluation of analgesia, but with animals close observation and skilful interpretation of behavioural responses are essential for a satisfactory recognition of pain (HELLEBRECKERS, 2001; WATERMAN-PEARSON, 2001). In our study we used the VAS, a scale approved in a lot of clinical studies both in human medicine as well in veterinary medicine (BRODBELT et al., 1997; DENEUCHE et al., 2004; SLINGSBY et al., 2006). To parameterize the behavioural data, we modified the Melbourne pain scale and we used it additionally to VAS to assess pain in dogs after total hip replacement. The Melbourne pain scale has been successfully used in several clinical studies to evaluate pain and compare the efficacy of different NSAIDs like ketoprofen or carprofen and opioids like butorphanol after surgery (PIBAROT et al., 1997; HOLTON et al., 1998a; DENEUCHE et al., 2004; LAREDO et al., 2004; HOELZER et al 2005). To avoid interobserver variability (HOLTON et al., 1998a) and to reduce bias, the study was blinded and just one observer performed the evaluations throughout the study.

In this study the pain scales used gave good results. They were easy to use, did not require much time and were inexpensive. However, the physiological parameters heart rate and respiratory rate, sometimes failed to give information about the patient's painful condition. Sixteen dogs (41 %), for example, panted at some point of the evaluations. Panting is common in dogs to ventilate dead space and to favour heat loss (ROBINSON 2003), but it is not necessarily an indicator of pain.

In panting dogs the respiratory rate was not considered for the evaluation. It seems, anyway, that respiratory rate and heart rate are good indicators of pain when patients are suffering severe pain.

The subjective mMPS assessment contains a lameness examination (Appendix 1). However, it has been seen that subjective gait evaluation must be interpreted cautiously and often does not agree with objective measurements (WAXMAN et al. 2008). To obtain more objective results we subjected all patients to a gait analysis on an instrumented treadmill. This non-invasive analysis provides objective information about the degree of the lameness and therefore renders an indirect parameter of pain (BENNETT et al., 1996; EVANS et al., 2005). The gait analysis has proven useful in the diagnosis of lameness and related pathologies as well as in the confirmation of success after orthopaedic surgery in dogs (MANLEY et al., 1990; McLAUGHIN et al., 1991; KENNEDY et al., 2003). However, in this study, the pain scales showed greater differences between groups compare to the gait analysis. A reason for that may be that different dog breeds with different body weights and, more importantly, with different types of gait were used. This resulted in an enormous variability between patients. To reduce the variability, we decided to consider only the hind legs. Vertical impulse and peak vertical forces were measured and a ratio between the values of the operated limb and the non operated limb was calculated. It would be expected that a dog receiving sufficient analgesics would keep this ratio constant. This was not entirely the case in our study but it could be noted that dogs in the group C reduced their ratio much more than dogs in the group M, and these differences were significant. Dogs receiving metamizole tended to distribute more weight on the operated limb than dogs in the group C. These results are an objective indicator that metamizole provided superior pain relief than carprofen in our study.

According to the results of the pain scales metamizole showed better and more satisfactory analgesia compared to carprofen after total hip replacement. Carprofen is a well recommended NSAID for postoperative pain alleviation, yet in our study three patients (15%) that had received carprofen needed rescue analgesia because of excessive pain (VAS over 50 and mMPS over 12). However, the rest of the carprofen group seemed to be adequately treated and did not show any unwanted side effects to the therapy. Metamizole on the other side gave

satisfactory pain relief to all patients, and showed significantly lower pain scores after T_3 for the mMPS and after T_{21} for VAS. However, it seems that acute postoperative treatment of pain was similar for both analgesics, because no statistical differences were seen during the first hours of the evaluation period. These results agree with findings in human medicine, where a single dose of metamizole in patients in moderate to severe postoperative acute pain supports good analgesia and is similar in efficacy compared to other analgesics like ibuprofen or diclofenac (REES et al., 2001; REES et al., 2002). However, other authors failed to find satisfactory results with metamizole when compared with other NSAIDs like meloxicam or diclofenac (CANDER et al., 2005; YILMAZ et al., 2006). As mentioned, carprofen is a well recognized analgesic to treat postoperative pain in dogs, especially if administered preemptively (NOLAN and REID, 1993; GRISNEUX et al., 1999; LASCELLES et al., 1998). It is therefore not surprising that there was no necessity for additional analgesia in 92.3% of the dogs. However, it is surprising that metamizole showed significantly better pain relief only after a couple of hours and not at the time of greatest postsurgical pain. Possible explanations for this fact include:

(1) During the first nine hours of pain evaluation the patients were in the recovery phase of anaesthesia. The mean of anaesthesia was 281.4 minutes, which most likely influences the following subjective pain evaluation. During the first six hours a lot of patients refused to stand up, maybe because of pain or maybe because they were simply still tired from their anaesthesia. Others may not have reacted to palpation of the wound because they were too tired to express their discomfort. The main problem is that pain scales in veterinary medicine lack sufficient accuracy (HOLTON et al., 1998a; HOLTON et al., 1998b) and may fail to detect some details that could make the difference between both groups in these extreme situations. This may lead to misinterpretation and inaccurate evaluation during the first postoperative hours.

(2) Another fact that could play an important role is the time of drug application. Carprofen was administered intravenously preoperatively, which means that once the surgeon began to operate, carprofen was already exerting an effect (DAHL et al., 1990; WOOLF et al., 1993). Metamizole on the other hand was given intravenously once the surgery

was finished. The patients receiving metamizole did not get any analgesic that blocked the production of inflammatory mediators (DRAY, 1995) and underwent the surgery with fentanyl as the only analgesic drug. This situation may have resulted in an advantage for the carprofen group during the first postoperative hours, because in the metamizole group there was no drug to decrease the intraoperative production and liberation of biochemical mediators. Despite of this the metamizole group showed satisfactory analgesia the whole study period,

(3) Another explanation of this phenomenon in the first postoperative hours may be that total hip replacement is a severely painful process (TRANQUILLI, 1997) that would need very potent analgesics during the first hours after surgery to see complete pain relief (KEHLET AND DAHL, 1993). In the early postoperative phase the endogenous mechanisms of pain control may not have been fully activated and the sole use of NSAIDs during this period may be of limited benefit. After a few hours the brainstem and its central control of pain become active, supporting the action of the analgesics present (MILLAN, 2002; MELLO AND DICKENSON, 2008). Metamizole may be potentiated by this mechanism to a greater extend than carprofen resulting in significant differences between groups after 21 (9) hours.

(4) Metamizole possesses an antihyperalgesic activity, probably through a modulatory effect on the central mechanism of pain control. This antihyperalgesic activity may be related to the ability of metamizole to inhibit mechanical nociception in spinal dorsal horn WDR neurons (VAZQUEZ et al., 1995). As mentioned earlier, WDR neurons, once they are sensitized, react to any stimulus and produce chronic central pain (DUBNER, 1990; ZHANG et al., 2005). Another characteristic that plays an important role in the prevention of hyperalgesic states is the blockade of NMDA receptors (WOOLF and THOMPSON, 1991). The study of BEIRITH et al. (1998) suggests that metamizole seems to have the ability to modulate excitatory amino acid release at the spinal cord, and a direct interaction with the binding of glutamate on its receptors may be part of the antihyperalgesic action of metamizole.

Metamizole did not exhibit significantly better results at all time points, but it showed a clear tendency towards a better outcome in all the patients evaluated. Research studies clearly show that the mechanism of action of metamizole is distinct from that of the "classical" NSAIDs. Since the exact mechanism of action of metamizole is still unclear, the explanations of its better analgesic action may be intriguing. Some authors postulate a strong PG inhibitory effect at central and peripheral levels, and others suggest a direct action in the PAG involving the opioidergic system and the central descending control of pain (LORENZETTI and FERREIRA, 1985; TORTORICI and VANEGAS, 1993; CHANDRASEKHARAN et al., 2002). One of the most mentioned and most discussed mechanism is the activation of the L-arginine/NO/cGMP pathway with the subsequent increased production of NO (LORENZETTI and FERREIRA, 1996; ALVES and DUARTE, 2002). The activation of the L-arginine-NO-cGMP pathway with resulting antinociception has been documented (DESOKY and FOUAD, 2005). There is, both in the periphery as well as in the CNS, a direct relationship between acute hypernociception blockade and the stimulation of the L-arginine-NO-cGMP pathway (KNOWLES et al., 1989; DUARTE et al., 1992; SACHS et al., 2003). However, the role of NO in nociception seems to be paradoxical, since the application of L-NAME (NOS inhibitor) leads to a decreased nociceptive response in rats (BUDAI et al., 1995) and farther, the intrathecal injection of NO-donating compounds like sodium nitroprusside (SNP) resulted in hyperalgesia in mice (KITTO et al., 1992). These findings do not agree with that of LORENZETTI and FERREIRA (1985) where the application of L-NAME reverted the analgesic effects of metamizole and given alone provoked hyperalgesia, suggesting that NO may have a participation in the antinociceptive activity of metamizole. BEIRITH et al. (1998) refuse this theory since in their experiments the application of NO inhibitors to mice did not influence the antinociceptive action of metamizole. As mentioned, NO seems to act both pronociceptive as well as antinociceptive, depending on the experimental model used to induce nociception as well as the route of drug administration. In humans it was demonstrated that NO acts pronociceptive when it is intracutaneously injected (HOLTHUSEN and ARNDT, 1994). In contrast, one study of IWAMOTO and MARION (1994) approved the hypothesis that the antinociception produced by muscarinic stimulation of the RVM is mediated by the L-arginine/NO/cGMP cascade. There is also evidence that NO mediates the

peripheral antinociceptive effect of some potent opioids like fentanyl or morphine (SONG et al., 1998; MAEGAWA and TONUSSI, 2003). All of these findings indicate that the L-arginine/NO/cGMP pathway is unlikely neither the only nor a direct mechanism of metamizole's analgesic action. However, one cannot deny that NO may at least partly mediate the antinociceptive activity of this drug.

The fact that metamizole modulates the excitatory amino acid release and that its antinociceptive properties depend on the NMDA receptors blockade, makes the L-arginine/NO/cGMP pathway more doubtful. Findings in slices of rat hippocampus suggest that NMDA receptor activation induces the generation of NO from arginine and mediates the increases in cGMP levels (EAST and GARTHWAITE, 1991). Furthermore the intrathecal injection of glutamate in mice produces hyperalgesia and this is largely mediated by the L-arginine-nitric oxide-cGMP pathway from both supraspinal and spinal sites (FERREIRA et al., 1999). Moreover in a study of MAURA et al. (2000) hyperalgesia produced by NMDA receptor agonists was blocked with the application of a NO synthase inhibitor Ng-nitro-L-arginine (L-NOARG). NO production appears to mediate NMDA-induced hyperalgesia and may contribute to other forms of centrally induced hypersensitivity (KITTO et al., 1992). From this it is difficult to relate the analgesic action of metamizole with NO production, especially if its antinociception may involve a direct interaction with glutamate receptors. Recently, findings of SIEBEL et al. (2004) further support the previous hypothesis that the antinociception caused by metamizole is associated with its interaction with the glutamatergic system, more specifically via interaction with the metabotropic glutamatergic system. In addition, they suggest a direct or indirect interaction of metamizole with a NK1-mediated pathway and with PKC-dependent mechanism. NK1 receptors are mostly distributed in Lamina I (MORRIS et al., 2004). In the superficial layer of the dorsal horn C- and A-fibres are inhibited by the descending control of the PAG (KOUTSILOU et al., 2007). This could explain why metamizole has the capacity to inhibit both somatic and visceral pain as well as first and second pain.

As mentioned before, the PAG and RVM are recognized as the central sites of action of analgesic agents like opioids and cyclooxygenase inhibitors (LEITH et al., 2007). The response to noxious stimuli can be further influenced by the recruitment of RVM ON-cells and OFF-cells. Nociceptive threshold is lowest

when the ON-cells population is active and OFF-cells are silent (HEINRICHER et al., 2009). Glutamatergic transmission blockade, and presumably blockade of ON-cells responses results in disfacilitation and thus reduction of the magnitude of noxious stimulus-elicited responses (JINKS, 2007). One consequence of these modulations is that the relationship between stimulus and response to pain is not always directly proportional. The response of output cells can be greatly altered via the interactions of various neurotransmitter systems in the spinal cord, all of which are subject to plasticity and alterations, particularly during pathological conditions (MELLO and DICKENSON, 2008). Pathological conditions may induce significant changes in the function of descending pain-modulatory pathways leading to facilitation or attenuation of nociception (VANEGAS and SCHAIBLE, 2004). As total hip replacement is an indication of coxarthrosis in dogs (MATIS, 1995) all patients involved in this study suffered from chronic painful arthritis. In one study of PINTO-RIBEIRO et al. (2008), rats with arthritis presented partly a different neurochemistry of descending antinociception compared to the control group, and the spontaneous activity of both pronociceptive ON-cells and antinociceptive OFF-cells was increased in arthritic rats. These findings could explain why patients respond differently to each analgesic therapy. In our study we saw that patients that received carprofen showed completely different behavioural responses. Some patients showed satisfaction and no pain with 4 mg kg^{-1} carprofen a day, while others seemed painful and it was necessary to treat them with rescue analgesia (3/20). Interestingly, all patients receiving metamizole showed a low variability in their pain scores. All of them presented low pain scores and therefore satisfactory pain relief. This may be due to a stronger activity of metamizole at central levels and its potential effects on medullary OFF- and ON-cells (TORTORICI and VANEGAS, 1993; TORTORICI et al., 1996). Carprofen as a COX-inhibitor reduces the PG production in the periphery (CURRY and COOK, 2005) and exerts spinal modulation through the COX-prostaglandin pathway in the PAG, which is also the target of μ-opioid analgesics (LEITH, 2007). However, there is no evidence of carprofen's effect on ON- or OFF-cells in the RVM. Because there is clinical evidence of synergic actions of NSAIDs and opioids (HELLYER, 1999; PIBAROT et al., 1997), presumably carprofen would have produced a better analgesia when combined with opioids.

Some patients presented unwanted side effects in this study: six dogs had diarrhoea; one of them belonged to the carprofen group and the rest to the metamizole group. Three dogs vomited and all of them were from the metamizole group. It seems like carprofen as a COX-2 inhibitor might be associated with less gastrointestinal side effects and discomfort than metamizole. Despite not being a potent COX-inhibitor, metamizole may produce stomach discomfort (nausea) (REES et al., 2001; REES et al., 2002). However, because of its gastrointestinal safety other authors recommend the use of metamizole in human patients where NSAIDs are contraindicated (BIANCHI et al., 1996). Metamizole does not produce GI ulcers and may even promote GI mucous blood flow (ERGÜN et al., 2001). Carprofen, on the other side, is a safe drug for chronic therapy in dogs (MANSA et al., 2007), but cases of GI ulcers produced by COX-2-inhibitors have been reported and care has to be taken when these drugs are chronically administered (LASCELLES et al., 2005; TERRENCE, 2006). Possibly the dose of metamizole used in this study – although recommended by the manufacturer - may provoke the described gastrointestinal side effects. More studies are warranted to evaluate the gastrointestinal safety of metamizole in this species.

Regardless of its mechanism of action, in our study the sole use of metamizole (50mg/kg) three times daily granted a satisfactory analgesia and clearly performed better than carprofen in all the evaluations made (pain scales and gait analysis) after total hip replacement in dogs. These results suggest that at the recommended dose, metamizole is a potent and satisfactory analgesic drug for use after orthopaedic surgery in dogs. The administration of 4 $mg \cdot kg^{-1}$ of carprofen as the sole analgesic after THR in dogs may not be sufficient in some patients. The possibility to combine NSAIDs like carprofen with non opioid analgesics like metamizole may be a good and safe alternative to treat both intra- as well as postoperative pain in dogs and this may serve especially useful in countries where opioids are not licensed in veterinary medicine. More studies will have to be performed to evaluate the efficacy and safety of this drug combination.

VII. ZUSAMMENFASSUNG

Evaluierung von Metamizol und Carprofen als postoperative Analgetika nach Hüftgelenksersatz bei Hunden.

Das Ziel dieser Studie war es, die analgetische Wirkung der von den jeweiligen Arzneimittelfirmen für den Hund empfohlenen Dosierungen von Metamizol im Vergleich zu Carprofen nach Hüftgelenkersatz zu bewerten. Es ist bekannt, dass Metamizol ein potentes Analgetikum beim Menschen ist. Bis heute gibt es keine Studien zur postoperativen Wirksamkeit von Metamizol beim Hund. Subjektive (Melbourne Schmerzskala (mMPS) und visuelle Analogskala (VAS)) und objektive (Ganganalyse, in welcher die vertikale Spitzenkraft (PVF) und der vertikale Impuls gemessen wurden) Bewertungsverfahren wurden in dieser Studie für die Evaluierung der Schmerzen herangezogen.

39 klinisch gesunde Hunde mit einem Körpergewicht zwischen 5,5 und 60,5 kg (keine Rassespezifität) wurden in diese Studie eingeschlossen. Die Hunde wurden nach Randomisierung in zwei Gruppen verteilt: Tiere der Gruppe M (n = 19) erhielten 50 $mg \cdot kg^{-1}$ IV Metamizol TID. Tiere der Gruppe C (n = 20) erhielten 4 $mg \cdot kg^{-1}$ Carprofen IV SID. Die Patienten wurden 3, 6, 9, 12, 20, 24, 28, 32, 36, 44, 48 and 56 Stunden nach Operationsende subjektiv beurteilt. Wurden bei der Evaluierung mittels mMPS bzw. VAS Punktwerte von 12 bzw. 50 Punkten überschritten, so wurde dies als Anzeichen von Schmerzen betrachtet, welche mit einer intravenösen Gabe von Buprenorphin, 10 $\mu g \cdot kg^{-1}$, behandelt wurden (rescue analgesia). Eine Ganganalyse wurde einmal präoperativ (preOP) und dann am ersten (OP1) und zweiten (OP2) postoperativen Tag durchgeführt.

Drei Patienten in der Gruppe C benötigten in den ersten 3 bis 6 postoperativen Stunden rescue analgesia. Keines der Tiere in Gruppe M benötigte die Gabe zusätzlicher Schmerzmittel. Sowohl bei der mMPS als auch bei der VAS zeigten Tiere der Gruppe M im Vergleich zu Gruppe C über den gesamten Zeitraum niedrigere Schmerz-Werte. Je nach verwendeter Schmerzskala waren diese Unterschiede nach 6 h (mMPS) bzw. nach 24 h (VAS) als signifikant zu betrachten ($p \leq 0.05$). Die postoperativen Ganganalysen zeigten bei Hunden der Gruppe M eine bessere Belastung der operierten Gliedmaße ($p \leq 0.05$).

Diese Ergebnisse zeigen, dass die alleinige Verwendung von Metamizol als Analgetikum eine potente und zufriedenstellende Analgesie nach orthopädischen Eingriffen bei Hunden gewährleistet. Des Weiteren wurde gezeigt, dass die alleinige Verwendung von Carprofen in der vom Hersteller empfohlenen Dosierung nach Hüftgelenksersatz bei Hunden nicht immer eine zufriedenstellende Analgesie hervorruft.

VIII. SUMMARY

Evaluation of Metamizole and Carprofen as postoperative analgesics in canine total hip replacement

The aim of this study was to evaluate the analgesic action of sodium metamizole compared to that of carprofen after THR in dogs at dosages recommended by their respective manufacturers. Metamizole is a potent analgesic in humans and until now there are no studies on its postoperative efficacy in dogs. In this study, multiple evaluation methods were used for pain assessment: two subjective pain scales, the modified Melbourne pain scale (mMPS) and the visual analogue scale (VAS). For objective assessment dogs were subjected to a gait analysis where peak vertical force (PVF) and vertical impulse (VI) were measured. 39 clinically healthy dogs weighing between 5.5 and 60.5 kg (no breed specificity) were enrolled in this study. Dogs were randomly distributed to two groups: dogs in group M (n = 19) received 50 $mg \cdot kg^{-1}$ IV metamizole TID and dogs in group C (n = 20) received carprofen (4 $mg \cdot kg^{-1}$ IV) SID. Dogs were subjectively evaluated 3, 6, 9, 12, 20, 24, 28, 32, 36, 44, 48 and 56 hours after the end of surgery. Dogs that scored more than 12 points on the mMPS or more than 50 points on the VAS were considered to be suffering from pain and received rescue analgesia (10 $\mu g \cdot kg^{-1}$ buprenorphine IV). Gait analysis was performed once preoperatively (preOP) and on the first (OP1) and second (OP2) postoperative day.

Three patients in group C needed rescue analgesia during the first 3 to 6 postoperative hours. Patients in group M did not need any additional analgesia. Modified MPS and VAS showed lower pain scores in group M compared to group C during the whole evaluation period. Depending on the pain scale used these differences became significant after 6 h (mMPS) or 24 h (VAS) ($p \leq 0.05$). Gait analysis revealed better loading of the operated leg for dogs in group M on both postoperative days ($p \leq 0.05$).

These results suggest that metamizole used alone is a potent analgesic drug which conveys satisfactory analgesia after orthopaedic surgery in dogs. On the other hand, at the dose recommended by the manufacturer carprofen does not always provide sufficient analgesia after THR in dogs.

IX. BIBLIOGRAPHY

Aigé V, Cruz JI. El dolor en los pequeños animales: bases neuroanatómicas, reconociemiento y tratamiento. Consulta difusa veterinaria 2001; 9(78): 63-70.

Allen K, DeCamp C, Bradent T, Bahns M. Kinematic gait analysis in healthy mixed breed dogs. V. C. O. T. Schattauer Publishers 1994; 7: 148-153.

Alves DP, Duarte IDG. Involvement of ATP-sensitive K channels in the peripheral antinociceptive effect induced by dipyrone. European Journal of Pharmacology 2002; 444: 47-52.

Ayoub SS, Botting RM, Goorha S, Colville-Nash PR, Willoughby DA, Ballou LR. Acetaminophen-induced hypothermia in mice is mediated by prostaglandins endoperoxide synthase 1 gene-derived protein. Proceedings of the National American Association 2004; 101(30): 11165-11169.

Beirith A, Santos A, Rodriguez A, Crecynski-pasa T, Calixto J. Spinal and supraspinal antinociceptive action of dipyrone in formalin, capsaicin and glutamate tests. Study of the mechanism of action. European Journal of Pharmacology 1998; 345: 233-245.

Bennett RL, DeCamp CE, Flo GL, Hauptmann JG, Stajich M. Kinematic gait analysis in dogs with hip dysplasia. American Journal of Veterinary Research 1996; 57(7): 966-971.

Bergmann MB, Nolte I, Kramer S. Comparison of analgesic efficacy of preoperative or postoperative carprofen with or without preincisional mepivacaine epidural anaesthesia in canine pelvic or femoral fracture repair. Veterinary Surgery 2007; 36: 623-632.

Bertram J, Lee D, Tofhunter R, Foel S, Williams A, Lust G. Multiple force platform analysis of the canine trot: a new approach to assessing basic characteristics of locomotion. V.C.O.T. Schattauer Publishers 1997; 10: 160-169.

Bianchi E, Leonardi L, Bregui E, Melanie P. Le scale del dolore como ausilio nell'interpretazione dello stato algico nel cane. Annali della facoltà di Medicina Veterinaria di Pisa 2003; 267-277.

Bianchi P, Ardizzone S, Petrillo M, Caruso I, Montrone F. Endoscopic assessment of the effects of dipyrone (metamizole) in comparison to paracetamol and placebo on the gastric and duodenal mucosa of healthy adult volunteers. Digestion 1996; 57: 186-190.

Botting R, Ayoub S. COX-3 and the mechanism of action of paracetamol/acetaminophen. Prostaglandins, Leukotriens and essential fatty acids 2005; 72: 85-87.

Brodbelt DC, Taylor PM, Stanway GW. A comparison of preoperative morphine and buprenorphine for postoperative analgesia for arthrotomy in dogs. Journal of Veterinary Pharmacology and Therapeutics 1997; 20: 284-289.

Budai D, Wilcox GL, Larson AA. Effects of nitric oxide availability on responses of spinal wide dynamic range neurons to excitatory amino acids. European Journal of Pharmacology 1995; 278: 39-47.

Budsberg SC, Verstraete MC, Soutas-Little RW. Force plate analysis of the walking gait healthy dogs. American Journal of Veterinary Research 1987; 48(6): 915-918.

Budsberg SC, Verstraete MC, Brown J, Reece L. Vertical loading rates in clinically normal dogs at a trot. American Journal of Veterinary Research 1995; 56(10): 1275-1280.

Budsberg SC, Chambers JN, Van Lue SL, Foutz TL, Reece L. Prospective evaluation of ground reaction forces in dogs undergoing unilateral total hip replacement. American Journal of Veterinary Research 1996; 57(12): 1781-1785.

Budsberg SC, Johnston SA, Schwarz PD, DeCamp CE, Claxton MS. Efficacy of etodolac for the treatment of osteoarthritis of the hip joints in dogs. Journal of the American Veterinary Medicine Association 1999; 214 (2): 206-210.

Cailliet R. Sindromes dolorosos: Dolor: mecamismos y manejo. 2. edition, Manual modermo, México, México; 1995; 300 p.

Campos C, De Greforio R, García-Nieto R, Gaco F, Ortiz P, Alemany S. Regulation of cicloogxgenana activity ba metamizole. European Journal of Pharmacology 1999; 378: 339-347.

Cander B, Girisgin S, Koylu R, Gul M, Kocak S. The effectiveness of analgesics in traumatic injuries of the extremities. Advanves in Therapy 2005; 22(5):462-466.

Carlsson KH, Jurna I. The role of descending inhibition in the antinociceptive effects of the pyrazolone derivatives, metamizole (dipyrone) and aminophenazone ("Pyramidon"). Naunyn-Schmiedeberg´s Archives Pharmacology 1987; 335:154-159.

Caron JP. Non-steroidal anti-inflammatory drugs. Proceeding of the annual convention of the AAEP 2000; 46: 243-249.

Caulcket N, Read M, Fowler D, Waldner C. A comparison of the analgesic effects of butorphanol with those of meloxicam after elective ovariohysterectomy in dogs. Canadian Veterinary Journal 2003; 44:565-570.

Chandrasekharan NV, Dai H, Lamar Turepu Roos K, Evanson NK, Tomsik J, Elton TS, Simons L. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression. Proceedings of the National Academy of Sciences of the United States of America 2002; 99(21): 13926-13931.

Célèrier E, Rivat C, Jun Y, Laulin JP, Larcher A. Long-lasting hyperalgesia induced by fentanyl in rats. Anaesthesiology 2000; 92(2): 465-472.

Cervero F, Gilbert R, Hammond RGE, Tanner J. Development of secondary hyperalgesia following non-painful thermal stimulation of the skin: psychophysical study in man. Pain 1993; 54: 181-189.

Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain 1993; 52: 259-285.

Cohen O, Zylber-Katz E, Caraco Y, Granit M, Levy M. Cerebrospinal fluid and plasma concentrations of dipyrone metabolites after a single oral dose of dipyrone. European Journal of Clinical Pharmacology 1998; 54: 549-553.

Curry SL, Cook JL. Nonsteroidal anti-inflammatory drugs: a review.

Journal of the American Animal Hospital Association 2005; 41: 298-309.

Dahl JB, Rosenberger J, Dirkes WE, Mogensen T, Kehlet H. Prevention of postoperative pain by balanced analgesia. British Journal of Anaesthesia 1990; 64: 518-520.

Dahl JB, Kehelt H. Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. British Journal of Anaesthesia 1991; 66: 703-712.

DeCamp CE, Soutas-Little RW, Hauptmann J, Olivier B, Braden T, Walton A. Kinematic gait analysis of the trot in healthy greyhounds. American Journal of Veterinary Research 1993; 54(4): 627-34.

DeCamp CE. Kinetic and Kinematic gait analysis and the assessment of lameness in the dog. The Veterinary Clinics of North America. Small Animal Practice 1997; 27(4): 825-840.

Degenaar JJ. Some philosophical considerations on pain. Pain 1979; 7: 281-304.

Deneuche AJ, Dufayet C, Goby L, Fayolle P, Desbois C. Analgesic comparison of meloxicam or ketoprofen for orthopaedic surgery in dogs. Veterinary Surgery 2004; 33: 650-660.

Desoky ES, Fouad IA. Pharmacological evidence for the role of nitric oxide-cGMP in antinociception. The Journal of Applied Research 2005; 5(3): 451-459.

Dickenson AH. Mechanisms of the analgesic actions of opiates and opioids. British Medical Bulletin 1991; 47(3): 690-702.

Dixon MJ, Taylo PM, Steagall PVM, Brondani JT, Luna SPL. Development of a pressure nociceptive threshold testing device for evaluation of analgesics in cats. Research in Veterinary Science 2007; 82: 85-92.

Dogan S, Vanderby R, Manley PA, Belloni LH, McBeath AA. Kinetic analysis of canine gait before and after total hip replacement. Abstracts-International Society of Biomechanics XII Congress 1989.

Dray A. Inflammatory mediators of pain. British Journal of Anaesthesia 1995; 75: 125-131.

Drogul A, Gülmez SE, Deveci MS, Gul H, Ossipov MH, Porreca F, Tuluna FC. The local antinociceptive actions of nonsteroidal anti-inflammatory drugs in the mouse radiant heat tail-flick test. Anaesthesia and Analgesia 2007; 104(4): 927-935.

Duarte ID, Dos Santos IR, Lorenzetti BB, Ferreira SH. Analgesia by direct antagonism of nociceptor sensitization involves the arginine-nitric oxide-cGMP pathway. European Journal of Pharmacology 1992; 217: 225-227, 1992.

Dubner R. Hyperalgesia and expanded receptive fields. Pain 1990; 48: 3-4.

East SJ, Garthwaite J. NMDA receptor activation in rat hippocampus induces cyclic GMP formation through the L-arginine-nitric oxide pathway. Neuroscience Letters 1991; 123(1): 17-19.

Edwards J, Meseguer F, Faura C, Moore R, McQuay H. Dipirona en dosis única para el dolor agudo postoperatorio. (Cochrane revision translated). La Biblioteca Cochrane Plus (ISSN 1745-9990) 2008; issue 3.

Egger CM, Glerum L, Haag KM, Rohbach BW. Efficacy and cost-effectiveness of transdermal fentanyl patches for the relief of post-operative pain in dogs after anterior cruciate ligament and pelvic limb repair. Veterinary Anaesthesia and Analgesia 2007; 34: 200-208.

Elphik MR, Schleiffer R. Comparative physiology of the L-arginine-nitric oxide pathway: an overview of a symposium at the 4th international congress of comparative physiology and biochemistry. Comparative Biochemistry and Physiology 1997; 118A(4): 921-923.

Ergün H, Hakki I, Cankat Tulunay F. Pharmacological characterization of metamizole-induced relaxation in phenylephrine-precontracted rabbit thoracic aorta smooth muscle. General Pharmacology. The vascular system 1999; 33: 237-241.

Ergün H, Gamze M, Apaydini I, Erçöçen AR, Tulunay FC. The effect of dipyrone on survival on skin flaps. Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery 2001; 35: 19-22.

Evans R, Horstman C, Conzemius M. Accuracy and optimization of force platform gait analysis in Labradors with cranial cruciate disease evaluated at a walking gait. Veterinary Surgery 2005; 34: 445-449.

Fachon L, Valette J-P, Sanaa M, Grandjean D. The measurement of ground reaction force in dogs trotting on a treadmill. An investigation on habituation. Veterinary and Comparative Orthopaedic and Traumatology 2006; 19: 81-86.

Ferreira J, Santos AR, Calixto JB. The role of systemic, spinal and supraspinal L-arginine-nitric oxide-cGMP pathway in thermal hyperalgesia caused by intrathecal injection of glutamate in mice. Neuropharmacology 1999; 38(6): 835-842.

Firth AM, Haldane SL. Development of a scale to evaluate postoperative pain in dogs. Journal of the American Veterinary Medical Association 1999; 214(5):651-659.

Fox SM, Mellor DJ, Lawoko CRO, Hodge H, Firth EC. Changes in plasma cortisol concentrations in bitches in response to different combinations of halothane and butorphanol, with or without ovariohysterectomy. Research in Veterinary Science 1998; 65:125-133, 1998.

García JR, Ynaraja E. El dolor en medicina de animales de compañia. Importancia clínica y razones para eliminarlo. *In*: Ynaraja E (ed.): Ciencias veterinarias volumen XXVI, asnestecia y analgésicos en animales de compañia. Publicación del consejo general de colegios veterinarios de España, Madrid, España 1999; 11-26.

Gaynor JS. Is postoperative pain management important in dogs and cats? Veterinary Medicine 1999; 94(3): 254-257.

Gehling M, Tryba M. Intrathekal verabreichtes Morphin bei orthopädischen Eingriffen. Optimierte Dosis bei Koanalgesie mit Metamizol. Anästhesist 2008; 57: 345-354.

Gülmez SE, Serel S, Uluç A, Can Z, Ergün H. Dipyrone increases the blood flow of arterial dorsal skin flaps. Aesthetic Plastic Surgery 2008; 32: 766-770.

Gonzalez de Mejía N. Analgesia multimodal postoperatoria. Revista de la Sociedad Española del Dolor 2005; 12: 112-118.

Greco D, Stabenfeldt G. Endocrinología: V. Las glándulas endocrinas y su función. *In*: Cunningham J (ed.): Fisiología Veterinaria. 3rd ed., Saunders, Madrid, Spain; 2003; 341-371.

Grimm KA, Wagner AE. Nervous system. *In*: Tranquilli JW, Thurmon JC and Grimm KA (eds.): Lumb and Johns'Veterinary Anesthesia and Analgesia. 4th ed., Blackwell publishing, Iowa, USA; 2007; 153-168.

Grisneaux E, Pibarot P, Dupuis J, Blais D. Comparison of ketoprofen and carprofen administered prior to orthopaedic surgery for control of postoperative pain in dogs. Journal of the American Veterinary Association 1999; 25(8): 1105-10.

Hansen BD, Hardie EM, Carroll GS. Physiological measurements after ovariohysterectomy in dogs: what's normal? Applied Animal Behaviour Science 1997; 51: 101 – 109.

Hansen BD. Assessment of pain in dogs: Veterinary clinical studies. ILAR Journal 2003; 44(3): 197-205.

Hardy JD, Harold GW, Goodell H. Experimental evidence on the nature of cutaneous hyperalgesia. The Journal of Clinical Investigation 1950; 29 (1): 115–140.

Heinricher MM, Martenson ME, Neubert MJ. Prostaglandin E2 in the midbrain periaqueductal gray produces hyperalgesia and activates pain-modulating circuitry in the rostral ventromedial medulla. Pain 2004; 110: 419-416.

Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: Specificity, recruitment and plasticity. Brain Research Reviews 2009; 60: 214-225.

Hellebreckers L. Manejo del dolor en la medicina veterinaria. Intermedica, Buenos Aires, Repuplica Argentina; 2002; 150 p.

Hellyer PW. Minimizing post-operative discomfort in dogs and cats. Veterinary Medicine 1999; 22: 259-266.

Hellyer PW. AAHA/AAFP Pain management guidelines for dogs and cats. Journal of the American Animal Hospital Association 2007; 43: 235-248.

Hinz B, Cheremina O, Bachmakov J, Renner B, Zolk O, Fromm M, Brune K. Dipyrone elicits substantial inhibition of peripheral cyclooxygenases in humans: new insights into the pharmacology of an old analgesic. The FASEB Journal. Research Communication 2007; 21: 2343-2351.

Hoelzler MG, Harvey RC, Lidbetter DA, Millis DL. Comparison of perioperative analgesic protocols for dogs undergoing tibial plateau levelling osteotomy. Veterinary Surgery 2005; 34: 337-344.

Hohm RB, Olmstead Ml, Matis U. Der Hüftgelenkersatz beim Hund. Tierärztliche Praxis 1986; 14:377-388.

Holthusen H, Arndt JO. Nitric oxide evokes pain in humans on intracutaneous injection. Neuroscience Letters 1994; 165(1-2): 71-74.

Holton LL, Scott EM, Nolan AM, Reid J, Welsh E, Flaherty D. Comparison of three methods used for assessment of pain in dogs. Journal of the American Veterinary Medical Association 1998a; 212: 61-66.

Holton LL, Scott EM, Nolan AM, Reid J, Welsh E. Relationship between physiological factors and clinical pain in dogs scored using a numerical rating scale. Journal of Small Animal Practice 1998b; 39: 469-474.

Hood D, Curry R, Eisenach J. intravenous remifentanil produced withdrawal hyperalgesia in volunteers with capsaicin-induced hyperalgesia. Anesthesia and Analgesia 2003; 97: 810-815.

Hutton WC, Freeman MA, Swanson SA. The force exerted by the pads of the walking dog. The Journal of Small Animal Practice 1969; 10(2): 71-77.

Ilkiw JE. Balanced anesthetic techniques in dogs and cats. Clinical Techniques in Small Animal Practice 1999; 14(1):27-37.

Iwamoto E, Marion L. Pharmacological evidence that nitric oxide mediates the antinociception produced by muscarinic agonists in the rostral ventral medulla of rats. Journal of Pharmacology and Experimental Therapeutics 1994; 269: 699-708.

Jevens DJ, Hauptman JG, DeCamp CE, Budsberg SC, Soutas-Little RW. Contribution to variance in force plate analysis of gait in dogs. The American Journal of Veterinary Research 1993; 54(4): 612-615.

Jin F, Chung F. Multimodal analgesia for postoperative pain control. Review article. Journal of Clinical Anaesthesia 2001; 13: 524-539.

Jinks SL, Carsten EE, Antoginini JF. Glutamate receptor blockade in the rostral ventromedial medulla reduces the force of multisegmental motor responses to supramaximal noxious stimuli. Neuroscience letters 2007; 426: 175-180.

Jones TL, Sweitzer SM, Wilson SP, Yeomas DC. Afferent fiber-selective shift in opiate potency following targeted opioid receptor knockdown. Pain 2003; 106:365-371.

Jurna I, Brune K. Central effect of the non-steroidal anti-inflammatory agents, indomethacin, ibuprofen, and diclofenac, determined in C fibre-evoked activity in single neurones of the rat thalamus. Pain 1990; 41: 71-80.

Kampe S, Warm M, Landwehr, S, Dastekin O, Haussmann S, Paul M, Pilgram B, Kiencke P. Clinical equivalence of IV paracetamol compared to IV dipyrone for postoperative analgesia after surgery for breast cancer. Current Medical Research and Opinion 2006; 22(10):1949-1954.

Kehlet H, Dahl JB. The value of “multimodal” or “balanced analgesia” in postoperative pain treatment. Review article. Anaesthesia and Analgesia 1993; 77: 1048-1056.

Keizer D, Van Wijhe M, Post WJ, Uges DRA, Wierda JMKH, Assessment of the clinical relevance of quantitative sensory testing with Von Frey monofilaments in patients with allodynia and neuropathic pain. A pilot study. European Journal of Anaesthesiology 2007; 24: 658-663.

Kennedy S, Lee DV, Lee JE, Lust G, Williams AJ, Soderholm LV, Hamilton S, Bliss SP, Dykes NL, Todhunter RJ. Gait evaluation in hip osteoarthritic and normal dogs using a serial force plate system. Veterinary and Comparative Orthopaedic Traumatology 2003; 16: 170-177.

Kitto KF, Haley JE, Wilcox GL. Involvement of nitric oxide in spinally mediated hyperalgesia in the mouse. Neuroscience Letters 1992; 148: 1-5.

Knowles RG, Palacios M, Palmer RM, Moncada S. Formation of nitric oxide from L-arginine in the central nervous system: a transduction mechanism for stimulation of the soluble guanylate cyclase. Proceedings of the National Academy of Science 1989; 86(13): 5159-5162.

Koppert W, Angst M, Alsheimer M; Sittl R, Albrecht S, Schüttler J, Schmelz M. Naloxone provokes similar pain facilitation as observed after short-term infusion of remifentanil in humans. Pain 2003; 106: 91-99.

Kosfeld HU. Der totale Hüftgelenkersatz beim Hund - klinische, röntgenologische und ganganalytische Erhebungen in den Jahren 1983 bis 1993. Diss med vet, München, 1996.

Koutsikou S, Parry DM, Mac Millan FM, Lumb B. Laminar organization of spinal dorsal horn neurones activated by C- vs. A-heat nociceptors and their descending control from the periaqueductal grey in the rat. European Journal of Neuroscience 2007; 26: 943-952.

Kramer M. Chronic toxicity of pyrazolones: the problem of nitrosation. British Journal of Clinical Pharmacology 1980; 10: 313-317.

Kukanich B, Lascelles BD, Papich MG. Use of a von Frey device for evaluation of pharmacokinetics and pharmacodynamics of morphine after intravenous administration as an infusion or multiple doses in dogs. American Journal of Veterinary Research 2005; 66(11): 1968-1974.

LaFuente MP, Franch J, Durall I, Díaz-Bertana C, Márquez R. Comparison between meloxicam and transdermally administered fentanyl for treatment of postoperative pain in dogs undergoing osteotomy of the tibia and fibula and placement of a uniplanar external distraction device. Journal of the American Veterinary Medical Association 2005; 227(11): 1768-1774.

Lamont LA, Tranquilli W, Grimm KA. Physiology of pain. Veterinary clinics of North America: Small animal practice 2000; 30(4): 703-728.

Landwehr S, Kiencke P, Gieseke T, Eggert D, Thuman G, Kampe S. A comparison between IV paracetamol and IV metamizole for postoperative analgesia after retinal surgery. Current Medical Research and Opinion 2005; 21(10):1569-1575.

Laredo FG, Belda E, Murciano J, Escobar M, Navarro A, Robinson KJ, Jones RS. Comparison of the analgesic effects of meloxicam and carprofen administered preoperatively to dogs undergoing orthopaedic surgery. The Veterinary Record 2004; 155: 667-671.

Lascelles BD, Butterworth SJ, Watermann AE. Postoperative analgesic and sedative effect of carprofen and pethidine in dogs. Veterinary Record 1994; 134: 187-191.

Lascelles BD, Watermann AE, Cripps PJ, Livingston A, Henderson G. Central sensitization as a result of surgical pain: investigation of the pre-emptive value of pethidine for ovariohysterectomy in the rat. Pain 1995; 62: 201-212.

Lascelles BD, Cripps PJ, Jones A, Waterman AE. Postoperative central hypersensitivity and pain: the pre-emptive value of pethidine for ovariohysterectomy. Pain 1997; 73: 461-471.

Lascelles BD, Cripps PJ, Jones A, Waterman-Pearson AE. Efficacy and kinetics of carprofen, administered preoperatively or postoperatively, for the prevention of pain in dogs undergoing ovariohysterectomy. Veterinary Surgery 1998; 27(6): 568-582.

Lascelles BD, Blikslager AT, Fox SM, Reece D. Gastrointestinal tract perforation in dogs treated with a selective cyclooxygenase-2 inhibitor: 29 cases (2002-2003).Journal of the American Veterinary Association 2005; 227(7):1112-7.

Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. Sleep Medicine Review 2006; 10: 357-369.

LeBars D, Gozariu M, Caddsen SW. Animal models of nociception. Pharmacological Reviews 2001; 53(4): 652 p.

LeBars D. The whole body receptive field of dorsal horn multireceptive neurones. Brain Research Review 2002; 40: 29-44.

Leece EA, Brearly JC, Harding EF. Comparison of carprofen and meloxicam for 72 hours following ovariohysterectomy in dogs. Veterinary Anaesthesia and Analgesia 2005; 32: 184-192.

Leith JL, Wilson AW, Donaldson LF, Lumb BW. Cyclooxygenase-1-derived prostaglandins in the periaqueductal gray differentially control C- versus A-fiber-evoked spinal nociception. The Journal of Neuroscience 2007; 27(42): 11296-11305.

Lemke KA. Understanding the pathophysiology of perioperative pain. The Canadian Veterinary Journal 2004; 45: 405-413.

Limpscomb VJ, Aliabadi FS, Lees P, Pead MJ, Muir P. Clinical efficacy and pharmacokinetics of carprofen in the treatment of dogs with osteoarthritis. The Veterinary Record 2002; 150: 684-689.

Lizarraga I, Chambers JP. Involvement of opioidergic and α_2-adrenergic mechanisms in the central analgesic effects of non-steroidal anti-inflammatory drugs in sheep. Research in Veterinary Science 2006; 80: 194-200.

Lopez-Muñoz J, Godínez-Chaparro B, Huerta-Cruz J, Guevara López U, Domínguez-Ramirez, Cortés-Arroyo A. The antinociceptive efficacy of morphine, metamizole, or their combination in an experimental rat model with different levels of inflammatory pain. Pharmacology, Biochemistry and Behaviour 2008; 91: 196-201.

Lord J, Waterfield A, Hughes J, Kosterlitz H. Endogenous opioid peptides: multiple agonists and receptors. Nature 1977; 267: 495-499.

Lorenzetti BB, Ferreira SH. Mode of action of dipyrone: direct antagonism of inflammatory hyperalgesia. European Journal of Pharmacology 1985; 114: 375-381.

Lorenzetti BB, Ferreira SH. Activation of the arginine-nitric oxide pathway in primary sensory neurons contributes to dipyrone-induced spinal and peripheral analgesia. Inflammation Research 1996; 45:308-311.

Lu Y, Sweitzer SM, Laurito CE, Yeomas DC. Differential opioid inhibition of C- and Aδ fiber mediated thermonociception after stimulation of the nucleus raphe magnus. Anaesthesia and Analgesia 2004; 98: 414-419.

Lumpkin EA, Caterina MJ. Mechanisms of sensory transduction in the skin. Nature 2007; 445: 858-865.

Luna S, Basílio AC, Steagal P, Machado L, Moutinho F, Takahira R, Brandao C. Evaluation of adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs. American Journal of Veterinary Research 2007; 68: 258-264.

Maegawa FAB, Tonussi CR. The L-arginine/nitric oxide/cyclic-GMP pathway apparently mediates the peripheral antihyperalgesic action of fentanyl in rats. Brazilian Journal of Medical and Biological Research 2003; 36: 1701-1707.

Maixner W, Dubner R, Bushnell MC, Kenshalo DR, Oliveras JL. Wide-dynamic dorsal horn neurons participate in the encoding process by which monkeys perceive the intensity of noxious heat stimuli. Brain Research 1986; 374: 385-388.

Manley PA, Vanderby R, Dogan S, Kohles SS, Mybeath AA. Ground reaction force comparison of canine cemented and cementless total hip replacement. Clinical Biomechanics 1990; 5: 199-204.

Mansa S, Palmér E, Grondahl C, Lonaas L, Nyman G. Long-term treatment with carprofen of 805 dogs with osteoarthritis. The Veterinary Record 2007; 160: 427-430.

Marinelli S, Vaughan CW, Schnell SA, Wessendorf MW, Christie MJ. Rostral ventromedial medulla neurons that project to the spinal cord express multiple opioid receptors phenotypes. The Journal of Neuroscience 2002; 22(24): 10847-10855.

Marnett LJ. Cyclooxygenase mechanisms. Current Opinion in Chemical Biology 2000; 4: 545-552.

Matis U. Operationsverfahren bei Hüftgelenksdysplasie. Tierärztliche Praxis 1995; 23: 426-31.

Maura G, Marcoli M, Pepicelli O, Rosu C, Viola C, Raiteri M. Serotonin inhibition of the NMDA receptor/nitric oxide/cyclic GMP pathway in human neocortex slices: involvement of 5-HT2c and 5-HT1a receptors. British Journal of Pharmacology 2000; 130: 1853-1858.

McLaughin R, Miller C, Taves C, Hearn T, Palmer N, Anderson G. Force plate analysis of triple pelvic osteotomy for treatment of canine hip dysplasia. Veterinary Surgery 1991; 20(5): 291-297.

Mello RD, Dickenson AH. Spinal mechanisms of pain. British journal of anaesthesia 2008; 101 (1): 8-16.

Millan MJ. Descending control of pain. Progress in Neurobiology 2002; 66: 355-474.

Morris R, Cheunsuang O, Sewart A, Maxwell D. Spinal dorsal horn neurone targets for nociceptive primary afferents: do single neurone morphological characteristics suggest how nociceptive information is processed at the spinal level. Brain Research Reviews 2004; 46: 173-190.

Morton DB, Griffiths PH. Guidelines on the recognition of pain, distress and discomfort in experimental animals and an hypothesis for assessment. The Veterinary Record 1985; 116(16): 431-436.

Muir WW, Woolf CJ. Mechanism of pain and their therapeutic implications. Journal of the American Veterinary Medical Association 2001; 219 (10): 1346-1356.

Nolan A, Reid J. Comparison of the postoperative analgesic and sedative effects of carprofen and papaveretum in the dog. The Veterinary Record 1993; 133(10):240-242.

Off W. Clinical and gaitanalytic evaluation of the excision arthroplasty of the hip in dogs and cats between 1978 and 1989. Diss med vet, Munich, 1992.

Off W, Matis U. Gait analysis in dogs. Tierärztliche Praxis 1997; 25(1): 8-14.

Off W, Matis U. Gait analysis in dogs 2: Installation of a gait analysis laboratory and locomotion studies. Tierärztliche Praxis 1997; 25(4): 303-311

Paulus HE, Withehouse MV. Nonsteroidal anti-inflammatory agents. Annual Review of Pharmacology 1973; 13: 107-125.

Perini RF, Wallace JL. Mucosal repair and COX-2 inhibition. Current Pharmaceutical Design 2003; 9(27). 2207-11.

Pibarot P, Dupuis J, Grisneaux E, Cuvelliez S, Planté J, Beauregard G, Bonneau NH, Bouffard J, Blais D. Comparison of ketoprofen, oxymorphone hydrochloride, and butorphanol in the treatment of postoperative pain in dogs. Journal of the American Veterinary Medical Association 1997, 211(4): 438-444.

Pierre SC, Schmidt R, Brenneis C, Michaelis M, Geisslinger G, Scholich K. Inhibition of Cyclooxgenases by dipyrone. Research paper. British Journal of Pharmacology 2007; 151: 494-503.

Pinto-Ribeiro F, Ansah O, Almeida A, Pertovaara A. Influence of arthritis on descending modulation of nociception from the paraventricular nucleus of the hypothalamus. Brain Research 2008; 63-75.

Pollmeier M, Toulemonde C, Fleishman, Hanson D. Clinical evaluation of firocoxib and carprofen for the treatment of dogs with osteoarthritis. The Veterinary Record 2006; 159: 547-551.

Poy NS, DeCamp CE, Bennett RL, Hauptman JG. Additional kinematic variables to describe differences in the trot between clinically normal dogs and dogs with hip dysplasia. American Journal of Veterinary Research 2000; 61(8): 974-978.

Raja SN, Campbell JN, Mexer RA. Evidence for different mechanisms of primary and secondary hyperalgesia following heat injury to the glabrous skin. Brain 1984; 107: 1179-1188.

Rawall N, Allvin R, Amilon A, Ohlsson T, Hallen J. Postoperative analgesia at home after ambulatory hand surgery: a controlled comparison of tramadol, metamizole and paracetamol. Anaesthesia and Analgesia 2001; 92: 347-351.

Rees J, Meseguer F, Faura C, Moore RA, McQuay H. Single doses dipyrone for acute postoperative pain. Cochrane Database of System Review 2001; (3): CDOO3227.

Rees J, Meseguer F, Faura C, Moore RA, McQuay H. Single doses of dipyrone for acute renal colic pain. Cochrane Database of System Review 2002; (4): CDOO3867.

Reese CJ, Trotter EJ, Short CE, Erb HN, Barlow LL. Assessing the efficacy of perioperative carprofen administration in dogs undergoing surgical repair of a rupture cranial cruciate ligament. Journal of American Animal Hospital Association 2001; 37(2): 115.

Remérand F, Le Tendre C, Baud A, Pourrat X, Favard L, Laffon M, Fusciardi J. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double blind study. Anaesthesia and Analgesia 2009; 109(6): 1963-1971.

Reuter BK, Asfaha S, Buret S, Sharkey KA, Wallace JL. Exacerbation of inflammation-associated colonic injury in rat through inhibition of cyclooxygenase-2. The Journal of Clinical Investigation 1996; 98:2067-85.

Rezende RM, França DS, Menezes GB, Dos Reis WGP, Bakhle YS, Francischi JN. Different mechanisms underlie the analgesic actions of paracetamol and dipyrone in a rat model of inflammatory pain. British Journal of Pharmacology 2008; 153: 760-768.

Richter T. Evaluierung von Metamizole vs. Fentanyl als intraoperative Analgesie – eine klinische Studie beim Hund. Diss Vet Med, München, 2007.

Riggs CM, DeCamp CE, Soutas-Little RW, Braden TD, Richter MA. Effects of subject velocity on force plate-measured ground reaction forces in healthy greyhounds at the trot. American Journal of Veterinary Research 1993; 54(9): 1523-1526.

Roberts II, Morrow J. Analgésicos-antipiréticos y antiinflmatorios, y farmacos antigotosos. *In*: Hardman J and Limbird L (eds.): Las bases farmacológicas de la terapéutica. Mc Graw Hill, Ciudad de Mexico, Mexico; 2001; 697-700.

Robinson E. Visión general de la función respiratoria: ventilación pulmonar. *In*: Cunningham JG (eds.): Fisiología veterinaria. Elsevier, Madrid, España; 2003; 469-470.

Rosa A, Massone F. Avaliação algimétrica por estímulo nociceptivo térmico e pressórico em cães pré-tratados com levomepromazina midazolam e quetamina associados ou não ao butorfanol ou buprenorfina. Acta Cirúrgica Brasileira 2005; 20(1): 39-45.

Roy WE. Examination of the canine locomotor system. The Veterinary Clinics of North America 1971; 1(1): 53-70.

Sachs D, Cunha F, Ferreira S. Peripheral analgesic blockade of hypernociception: activation of arginine/NO/cGMP/protein kinase G/ATP-sensitive K channel pathway. Proceedings of the National Academy of Science 2003; 101(10): 3680-3685.

Sánchez S, Martín MJ, Ortiz P, Motilva V, Herrerías JM, Alarcón de la Lastra C. Role of prostaglandins and nitric oxide in gastric damage induced by metamizole in rats. Inflammation Research 2002a; 51: 385-392.

Sánchez S, Alarcón de la Lastra C, Ortiz P, Motilva V, José Martín M. Gastrointestinal tolerability of metamizole, acetaminophen and diclofenac in subchronic treatment in rats. Digestive Diseases and Sciences 2002b; 47(12): 2791-2798.

Schebitz H, Brass W. Operationen an Hund und Katze. 2. ed., Parey editorial, Berlin, Germany; 1999; 453 p.

Schroeder RA, Kuo PC. Nitric oxide: Physiology and pharmacology. Anaesthesia and Analgesia 1995; 81: 1052-1059.

Shafford HL, Lascelles BD, Hellyer PW. Pre-emptive analgesia: managing pain before it begins. Veterinary Medicine 2001; 94: 478-492.

Shug SA. Update on the role of non-opioids for postoperative pain treatment. Best practice & Research 2007; 21(1): 15-30.

Siebel J, Beirith A, Calixto J. Evidence for the involvement of metabotropic glutamatergic, neurokinin 1 receptor pathways and protein kinase C in the antinociceptive effect of dipyrone in mice. Brain Research 2004; 1003: 61-67.

Simonet G, Rivat C. Opioid-induced hyperalgesia: abnormal or normal pain? Neuroreport 2003; 14(1): 1-7.

Syngelyn FJ, Governeur JM. Postoperative analgesia after total hip arthroplasty: i.v. PCA with morphine, patient-controlled epidural analgesia, or continuous “3-in-1” block?: a prospective evaluation by our acute pain service in more than 1,300 patients. Journal of Clinical Anaesthesia 1999; 11(7): 550-4.

Slingsby LS, Jones A, Waterman-Pearson AE. Use of a new finger-mounted device to compare mechanical nociceptive thresholds in cats give pethidine or no medication after castration. Research in Veterinary Science 2001; 70: 143-346.

Slingsby LS, Murison JM, Goessen L, Engelen M, Waterman-Pearson AE. A comparison between pre-operative carprofen and a long-acting sufentanil formulation for analgesia after ovariohysterectomy in dogs. Veterinary Anaesthesia and Analgesia 2006; 33: 313 – 327.

Song HK, Pan HL, Eisenbach J. Spinal nitric oxide mediates antinociception from intravenous morphine. Anaesthesiology 1998; 89(1): 215-221.

Stasiak KL, French E, Hellyer PW, VandeWoude S. Species-specific assessment of pain in laboratory animals. Contemporary Topics in Laboratory Animal Science 2003; 42 (4): 13-20.

Stramer UM, Höthker F, Lehnen K, Stüber F. Postoperative analgesia with tramadol and metamizole. Continual infusion versus patient controlled analgesia. Anästhesist 2003; 52(1): 33-41.

Stamford JA. Descending control of pain. British Journal of Anaesthesia 1995; 75: 217-227.

Stoelting RK, Hillier SC. Pain. *In*: Stoelting RK and Hillier SC (eds.): Pharmacology and Physiology in anaesthetic practice. 4th ed., Philadelphia, USA; 2006; 715-716.

Tavares I, Lima D. From the neuroanatomy to gene therapy: searching for new ways to manipulate the supraspinal endogenous pain modulatory system. Journal of Anatomy 2007; 211: 261.268.

Taylor PM, Steagall PVM, Dixon MJ, Ferreira TH, Luna SPL. Carprofen and buprenorphine prevent hyperalgesia in a model of inflammatory pain in cats. Research in Veterinary Science 2007; 87: 369-375.

Terrence PC. The clinical pharmacology of cyclooxygenase-2-selective and dual inhibitors. Veterinary Clinic of Small Animal practice 2006; 36: 1061-1085.

Todd AJ. Anatomy of primary afferents and projections neurones in the rat spinal dorsal horn with particular emphasis on substance P and the neurokinin receptor. Experimental physiology 2002; 87(2): 245-249.

Torebjörk HE, Lundberg LE, Lamotte RH. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. Journal of Physiology 1992; 448: 765-780.

Torregrosa S. Mecanismo y vías del dolor. Boletín escuela de medicina, P Universidad Católica de Chile, Santiago, Chile; 1994; 202-206.

Torres L, Rodriguez MJ, Montero A, Herrera J, Calderon E, Cabrera J, Porres R, de la Torre MR, Martinez T, Gomez JL, Ruiz J, Garcia-Magaz I, Camara J. Ortiz P. Efficacy and safety of dipyrone versus tramadol in the management of pain after hysterectomy: a randomized, double-blind, multicenter study. Regional Anaesthesia and Pain Medicine 2001; 26(2):118-124.

Tortorici V, Vanegas H. Putative role of medullary off- and on-cells in the antinociception produced by dipyrone (metamizole) administered systemically or microinjected into PAG. Pain 1993; 57: 197-205.

Tortorici V, Vázquez E, Vanegas H. Naloxone partial reversal of the antinociception produced by dipyrone microinjected into the periaqueductal gray of rats. Possible involvement of medullary off- and on-cells. Brain Research 1996; 725: 106-110.

Tranquilli WJ, Grimm KA, Lamont LA. Manual de consulta rápida. Tratamiento del dolor en pequeños animales. 1st ed., Multimedica, Barcelona, Spain; 2001; 120 p.

Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. Annual Review of Pharmacology and Toxicology 1998; 38: 97-120.

Vanegas H, Schaible HG. Prostaglandins and cyclooxygenases in the spinal cord. Progress in Neurobiology 2001; 64: 327-363.

Vanegas H, Schaible H. Descending control of persistent pain: inhibitory or facilitatory? Review. Brain Research 2004; 46(3): 295-309.

Vanegas H, Tortorici V. Opioidergic effects of nonopioid analgesics on the central nervous system. Cellular and molecular neurobiology 2002; 22(5/6): 655-661.

Vaughan CW, Ingram SL, Connoer MA, Christie MJ. How opioids inhibit GABA-mediated neurotransmission. Letters to nature 1997; 390: 611-614.

Vazquez E, Hernandez N, Escobar W, Vanegas H. Antinociception induced by intravenous dipyrone (metamizole) upon dorsal horn: Involvement of endogenous opioids at the periaqueductal gray matter, the nucleus raphe magnus, and the spinal cord in rats. Brain Research 2005; 1048: 211-217.

Vlahov V, Badian M, Verho M, Bacracheva N. Pharmacokinetic of metamizole metabolites in healthy subjects after a single oral dose of metamizole sodium. European Journal of Pharmacology 1990; 38: 61-65.

Volz M, Kellner HM. Kinetics and metabolism of pyrazolones (propyphenazone, aminopyrine and dipyrone). British Journal of Pharmacology 1980; 10: 299-308.

Waterman-Pearson AE. Analgesia. *In:* Seymour C and Gleed R (eds.): Manual de anestecia y analgesia en pequeños animales. S ed., Barcelona, Spain; 2001; 79-94.

Waxman AS, Robinson DA, Evans RB, Hulse DA, Innes JF, Conzemius MG. Relationship between objective and subjective assessment of limb function in normal dogs with an experimentally induced lameness. Veterinary Surgery 2008; 37: 241-246.

Wolfe M, Lichtenstein D, Singh G. Gastrointestinal toxicity of non-steroidal-anti-inflammatory drugs. The New England Journal of Medicine 1999; 341(7): 1888-1899.

Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983; 306 (15): 686-688.

Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl –D-aspartic acid receptor activation; implications for the treatments of post-injury pain hypersensitivity states. Pain 1991; 44: 293-299.

Woolf CJ, Chong MS. Preemptive analgesia –treating postoperative pain by preventing the establishment of central sensitization. Anaesthesia and Analgesia 1993; 77: 362-379.

Yilmaz I, Sener M, Yavuz H, Yilmazer C, Erkan A, Cagici C, Gencay S, Caliskan E, Ozluoglu L. Postoperative pain management in clinics of otolaryngology. Kulak Burun Bogaz Ihtisas Dergisi 2006; 16(1):1-6.

Zamuner SR, Warrier N, Buget AG, MacNaughton WK, Wallace JL. Cyclooxygenase-2 mediates post- inflammatory colonic secretory and barrier dysfunction. Functional bowel disease 2003; 52: 1714-1720.

Zhang H, Xie W, Xie Y. Spinal cord injury triggers sensitization of wide dynamic range dorsal horn neurons in segments rostral to the injury. Brain Research 2005; 1055: 103-110.

Zylber-Katz E, Granit L, Levy M. Plasma binding of dipyrone metabolites in man. European Journal of Clinical Pharmacology 1985; 29: 61-67.

Zylber-Katz E, Granit L, Levy M. Formation and excretion of dipyrone metabolites in man. European Journal of Clinical Pharmacology 1992; 42: 187-191.

X. APPENDIX

Physiologic data		
	Percentage in increase in heart rate relative to preprocedural rate	
	> 20%	1
	> 50%	2
	> 100%	3
	Percentage in increase in respiratory rate relative to preprocedural rate	
	> 20%	1
	> 50%	2
	> 100%	3
Response to palpation		
	No change ti preprocedural behavior	0
	Guards/reacts when touched	2
	Guards/reacts before touched	3
Activity		
	At rest - (sleeping/semiconscious	0
	At rest – (awake/eating)	0
	Restless (pacing continuously, getting up and down)	2
	Rolling, trashing	3
Posture		
	Guarding or protecting affected area (includes fetal position)	2
	Lateral/sternal recumbency	0
	Sitting or standing, head up	1
	Standing, head hanging down	2
	Moving	1
	Abnormal position (eg. Prayer position, hunched back)	3
Vocalization		
	Not vocalizing	0
	Vocalizing when touched	2
	Intermittent vocalization	2
	Continuous vocalization	3
Response to manipulation		
	No response	0
	Mild to moderate resistance	1
	Sever resistance	2
	Does not tolerate any manipulation	3
Leading out of the kennel		
	Walks normaly	0
	Laming	1
	Stiffing	2
	It refuses to move	3

Appendix 1: modified Melbourne pain scale (mMPS)

XI. ACKNOWLEDGEMENTS

In the first place, I would like to thank Prof. Dr. med. vet. Dr. med. vet. habil. U. Matis, for trusting in me and giving me the possibility to work on such an interesting topic.

Then also, very special thanks go to Dr. med. vet. Korbinian Pieper for instructing me and explaining me this work in every detail, without hesitation at any time. I would also like to thank him for the continued emotional and physical support during the study and for his willingness to be always ready to help, no matter what the problem is. I would also like to say that for me working with him was a privilege and a pleasure. I can not fail to mention that I am extremely grateful for everything that he taught me and he is partly responsible for me trying to stay and excel in anaesthetic training.

I would also like to express special thanks to all colleagues who made this work possible, especially to my dear fellows, Dr. med. vet. Tanja Richter and Dr, med. vet. Andreas Raith. Both were always willing to help me and supported my work every day. I would like to take this opportunity to thank them for all that I learned and for the time they took to teach me everything.

Furthermore I would like to thank Stephanie Steigmeier for introducing me into the world of the gait analysis and for helping me to process the data. I also would like to thank PD. Dr. med. vet. Sven Reese for his support and advice with the statistical analysis.

Finally I would like to thank my family for the whole support, despite being far away from here. They trusted in me from the very beginning and they were always there to give warm and close encouragement during my stay in Germany, away from home.