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Perineural dexmedetomidine combined with bupivacaine on sciatic/femoral nerve blocks in dogs undergoing stifle joint surgery

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CICLO XXXI

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Sommario

Scopo del lavoro

L'obiettivo di questo studio è quello di valutare la durata dei blocchi motorio e sensitivo, la qualità dell'anestesia e dell'analgesia dopo il blocco neuro-stimolato dei nervi sciatico e femorale, utilizzando solo bupivacaina o combinandola con la dexmedetomidina, in cani sottoposti a procedure chirurgiche interessanti l'articolazione del ginocchio.

Materiali e metodi

Trentuno cani, di 4.4 anni (1-11) e di peso 25.2 kg (3-68), assegnati in maniera random a tre gruppi: A, B e C. Il Gruppo A riceveva bupivacaina 0,25 $mgkg^{-1}$ per ogni nervo; il Gruppo B riceveva bupivacaina 0,25 $mgkg^{-1}$ con dexmedetomidina 0,25 μgkg^{-1} per ogni nervo; il Gruppo C riceveva bupivacaina 0,5 $mgkg^{-1}$ per ogni nervo.

I dati raccolti durante l'anestesia sono stati: frequenza cardiaca (HR), frequenza respiratoria (RR), pressione media (MAP), anidride carbonica a fine espirazione ($EtCO_2$), end-tidal isofluorano (EtISO), temperature esofagea (T°).

Sono stati registrati anche i tempi di durata di chirurgia, anestesia ed estubazione.

La Short Form della Glasgow Composite Pain Scale (GCPS-SF score) è stata usata per valutare il dolore post-operatorio a 1, 2, 4, 6, 8, 12, 16 e 20 dall'estubazione

La capacità di camminare, la propriocezione e il pinch test sono stati usati per valutare la durata del blocco motorio e sensitivo ad ogni ora dopo l'estubazione e fino alla fine del blocco.

Risultati

Il test della normalità di Shapiro-Wilk mostra che i dati non sono normalmente distribuiti.
Differenze significative sono state trovate tra i gruppi in relazione al peso corporeo, ma non per BCS ed età.
Le frequenze cardiache e respiratorie restano nei ranges fisiologici in tutti i gruppi.
La pressione arteriale è stata variabile nei differenti punti della procedura; è stato necessario somministrare una fluidoterapia di supporto in quasi tutti gli individui del Gruppo C, per compensare la moderata ipotensione perianestetica.
L'analisi statistica dei punteggi del dolore mostra che c'è una differenza significativa alla 16° ora rispetto alla 1° nel Gruppo B, e alla 16° e 20° ora nel Gruppo C; nessuna differenza è stata trovata nel Gruppo A.
Nessuna differenza significativa è stata trovata tra i gruppi per quanto concerne la durata dei blocchi motorio e sensitivo.
Nel Gruppo B sono state trovate correlazioni tra la durata dei blocchi motorio e sensitivo e il peso corporeo dei soggetti.

Conclusioni

Sulla base dei risultati preliminari di questo studio, la combinazione di bupivacaina e dexmedetomidina usata per il blocco perineurale dei nervi sciatico e femorale (0,25 $mgkg^{-1}$ and 0,25 μgkg^{-1} rispettivamente per ogni nervo) potrebbe significativamente aumentare la durata del blocco e apportare dei benefici sulla stabilità della pressione arteriale. Per confermare statisticamente la tendenza trovata con i nostri risultati, è necessario un campione di studio più grande e omogeneo.

Abstract

Objective

The aim of this study is to evaluate the motor and sensitive block duration, related to quality of anaesthesia and analgesia after sciatic/femoral electrolocation nerve block with bupivacaine alone and in combination with dexmedetomidine in dogs undergoing unilateral stifle joint surgery.

Materials and methods

Thirty-one dogs, median age 4.4 years (1 – 11) and median weight 25.2 kg (3 - 68), randomly assigned to three groups: A, B and C. Group A received bupivacaine 0,25 $mgkg^{-1}$ to each nerve; Group B received bupivacaine 0,25 $mgkg^{-1}$ mixed with dexmedetomidine 0,25 μgkg^{-1} to each nerve; Group C received bupivacaine 0,5 $mgkg^{-1}$ to each nerve.

Data recorded over all the anaesthesia procedure were: heart rate (HR), respiratory rate (RR), median blood pressure (MAP), carbon dioxide end-tidal ($EtCO_2$), end-tidal isoflurane (EtISO), esophageal temperature (T°).

Surgery, anaesthesia and extubation times were also collected.

Short Form of the Glasgow Composite Pain Scale (GCPS-SF score) was used to assess post-operative pain at 1, 2, 4, 6, 8, 12, 16 e 20 hours after extubation.

Ability to walk, proprioception and pinch test were used to assess motor and sensory block duration every one hour after the extubation and until blockade end.

Results

Shapiro-Wilk normality test shows that data were not normally distributed.
Significant differences were found among groups in relation of body weight, but not for BCS and age.
Heart and respiratory rates remained in physiological ranges in all three groups. Arterial pressure was variable along the different points of the procedure; fluid therapy support was necessary in almost all individuals for Group C to compensate a mild perianaesthetic hypotension.
Pain score was increased at 16^{th} hour compared to the 1^{st} hour in Group B, and at 16^{th} and 20^{th} hours compared to the 1^{st} in Group C; no differences are found in Group A.
No significant difference were found between groups concerning motor and sensory blocks duration. Between motor and sensory block scores and dogs weights there were some correlations in Group B.

Conclusions

On the basis of the preliminary results of this study, the mixture of bupivacaine and dexmedetomidine used for perineural blockage of the sciatic and femoral nerves (0,25 $mgkg^{-1}$ and 0,25 μgkg^{-1} respectively for each nerve) can significantly increase the blockade duration and improving some benefits on arterial pressure stability. To statistically confirm the tendence found by our results a larger and homogenous sample will be indispensable.

Introduction

Animal welfare is nowadays considered an essential point for the correct management of the patient, for various needs, as surgical, oncology, obstetric or medical services.

For this reason, the efforts in findings anaesthetic and analgesic protocols, able to adapt to different needs and situations is mandatory.

Pain is defined in 1979 by the International Association for the Study of Pain (IASP) as "*Unpleasant sensory and emotional experience associated with actual or potential tissue damage, or describe in terms of such damage".*[(1)]

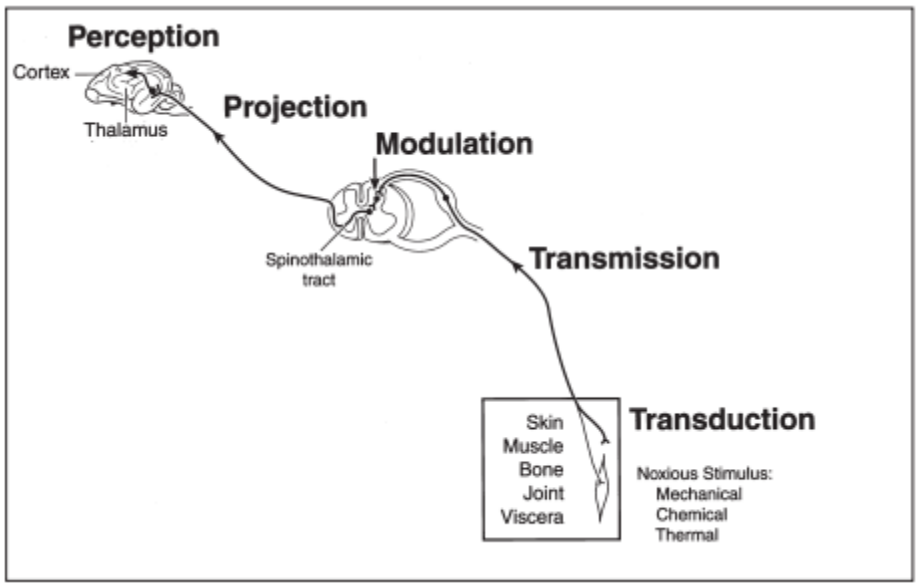
Recently, in 2016, Williams and Craig proposed another definition of pain as "*a distressing experience associated with actual or potential tissue damage, with sensory, emotional, cognitive and social components".* It effectively describes the subjectivity of pain experience, differentiating it from physiological processes, although biological mechanisms govern that experience.[(2)]

An unpleasant emotional experience (eg, fear) can be the trigger of homeostatic responses similar to those induced by noxious stimuli, characterized by reflex withdrawal, behavioral, autonomic nervous system, neuroendocrine, and immune system responses.[(3)]

1. Mechanism of pain

Pain sensation involves different physiologic processes as stimuli transduction, transmission, modulation, projection, and perception.

The ***transduction*** occurs when a stimulus activates nociceptors and high-threshold sensory nerve fibres, warning the organism of a potentially damaging event.[3]



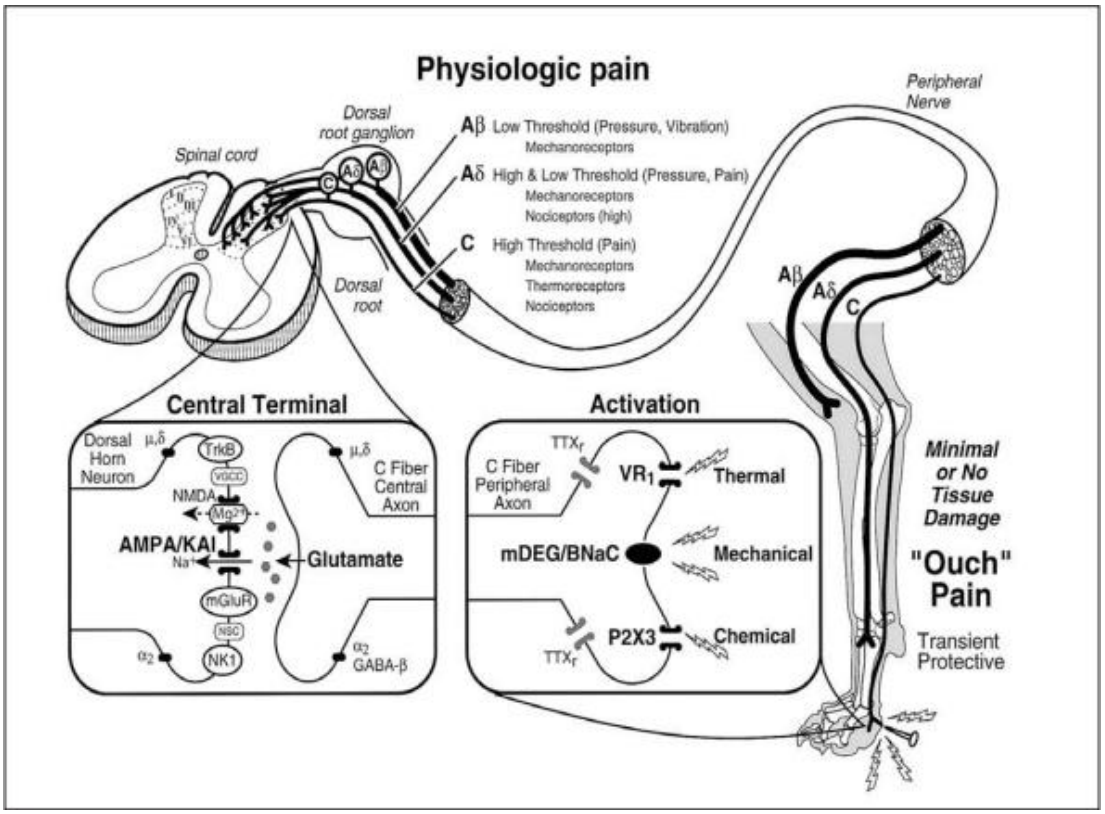
(from: Muir WW, Woolf CJ. Mechanisms of pain and their therapeutic implications. J Am Vet Med Assoc 219:1346, 2001)

Nociceptors can be classified in several ways:

1) on the basis of their responsiveness to the various stimulation modalities in:
   - *mechanical*,
   - *thermal*,
   - *chemical;*
2) on the basis of the structure of their axons in:
   - *myelinated* (A-fiber), usually characterized by thin axons with fast conduction velocities (2-25 m/s). There is a small percentage of A-fiber nociceptors that have faster conduction velocities, up to 50m/s;
   - *unmyelinated* (C-fiber), with a slow conduction velocities ranging from 0.3-2.0 m/s.

Not all A and C-fibres sensory receptors are nociceptive.[4]

Nociceptors encode the intensity, duration, location, and quality of the noxious stimulus and, once activated, transduce noxious stimuli into depolarizing electrical potentials; after that moment, the **transmission** of the stimulus to the spinal cord can occurs.[3]



(from: Muir WW, Woolf CJ. Mechanisms of pain and their therapeutic implications. J Am Vet Med Assoc 219:1346, 2001)

Many of the C and finely A fibers contain the excitatory amino acids aspartate (NMDA) and glutamate and a wide variety of neuropeptides, including substance P, calcitonin gene-related peptide, cholecystokinin (CCK), galanin, somatostatin, and others, that are selectively released in the spinal dorsal horn and in peripheral tissue.[5]

The dorsal horn of the spinal cord is divided into laminae based on the types of neurons and their organization:

- *lamina I* (the marginal zone),

- *lamina II* (substantia gelatinosa)
- *laminae III –VI* (nucleus proprius)
- *lamina X* (the area around the central canal)

The target of somatic C nociceptors is ipsilateral lamina II, whereas Aδ nociceptors terminate in ipsilateral lamina I and, to a lesser extent, lamina V; the large Aβ sensory nerve fibres terminate on neurons predominantly located in laminae III, IV, and V.[3,5]

Visceral C nociceptors have a more diffuse projection to lamina II that is spread out over several segments, as well as bilateral projections to laminae V and X. The widespread distribution of the visceral C fibers may explain the diffuse quality of visceral pain.[5]

In the laminae can be distinguished two kind of neurons:

- *nociceptive specific neurons* (NS): are so-named because they receive peripheral input exclusively from nociceptive afferents; they are excited by both A-δ and C fibers. NS neurons are located mainly in lamina I and II of the dorsal horn; they are present in lesser number in lamina V;
- *wide dynamic range neurons* (WDR): are so-named because they receive input from large diameter, non-nociceptive afferents, as well as both A-δ and C fibers. They are concentrated in deeper layers of the dorsal horn (lamina V and VI) but are also found in smaller numbers in I, II, and IV.[6]

In spinal cord, **modulation** of sensory informations takes place, before these are relayed to the brain. All afferent sensory nerve fibers that enter the spinal cord are separated in order to innervate second-order neurons in the different zones or laminae of the gray matter of the dorsal horn of the spinal cord. The dorsal horn laminae comprise layers of functionally distinct cells that form columns extending the length of the spinal cord. The columns contain a large number of second-order excitatory and inhibitory interneurons that receive multiple inputs from surrounding columns and send outputs to the brain and to the ventral (motor) horn. The ventral horn contains interneurons and motor neurons that control the muscles of the trunk and limbs, whereas the transition zone between the dorsal and ventral horn (in

thoracic and sacral cord segments) contains autonomic preganglionic neurons that mediate involuntary (visceral) functions and transmit some sensory afferent information via multiple parallel circuits to the brain.[3]

The Aδ- and C fibres input to the dorsal horn releases glutamate that preferentially binds to α-amino-3 hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA), kainite, and Nmethyl-D-aspartate (NMDA) ligand-gated sodium and calcium channels. Under normal conditions, NMDA ion channels are blocked by magnesium ion (Mg2+). Activation of AMPA receptor ion channels depolarizes the membrane, producing fast excitatory postsynaptic potentials that are focused by local and descending inhibitory neurons, many of which release the inhibitory substances glycine and γ-aminobutyric acid (GABA). Fast excitatory potentials carried predominantly by A-δ sensory nerve fibres signal the onset, duration, and location of the noxious stimulus and are responsible for the well localized and relatively transient sharp, pricking, stinging, and stabbing pain that serves to warn and protect the animal from additional tissue damage. Intense thermal or mechanical stimulation increases the quantity of glutamate and substance P released from afferent sensory nerve terminals, activating postsynaptic neurokinin-1 and metabotropic glutamate receptors (mGluR), facilitating and prolonging the release of intracellular calcium and generating plateau potentials by activation of VGCC (voltage-gated calcium channels) and nonspecific cation channels. The magnitude of these events is proportional to stimulus intensity and is responsible for the removal of the magnesium blocking of NMDA receptors and the generation of a greater and longer (> 10 seconds) postsynaptic depolarizing response, such that pain remains long after the stimulus is removed. [3]

Once sensory informations are processed, the **projection** phase starts. WDR and NS axons cross to the opposite side of the spinal cord, ascend in the anterolateral quadrant and terminate primarily in the thalamus. This pathway is called the lateral spinothalamic tract. Neurons in the thalamus receiving messages along this tract subsequently project their axons upward to a number of cerebral cortex locations including the primary somatosensory cortex. There are numerous other terminations of spinal cord pain projection neurons throughout the midbrain, pons and medulla.

Spinal cord pain projection neurons do not project only to those areas of the thalamus which relay pain messages to primary somatosensory cortex. In addition, the anterolateral quadrant which contains the lateral spinothalamic tract is not the sole pathway for transmission of pain messages to levels above the spinal cord.(6)
The ascending pain pathways are summarized in the table below.

Ascending Pain Pathways

Pathway	*Origin*	*Cord Location*	*Initial Destination*	*Roles*	*Final Destination*
Spinothalamic medial division	Deep dorsal horn Lamina VI-VIII WDR and NS neurons	Anterolateral quadrant	Medial thalamus (intralaminar nuclei nuc submedius)	Arousal, emotional Motor responses Affective-motivational responses Somatosensory cortex Visual cortex	Prefrontal cortex Primary motor cortex Basal ganglia
lateral division	Lamina I, IV-VI (2/3 from I, V) WDR and NS neurons	Anterolateral quadrant	Lateral thalamus (VPL, VB, PO)	Sensory-discriminative	Somatosensory cortex Retroinsular cortex
Spinomesencephalic	Lamina I, IV-VII	Anterolateral quadrant	Periaqueductal grey sup. Colliculus n. Edinger Westphal n Darkschwitz n cuneiformis	Unpleasantness/fear Centrifugal control Orientation toward painful stimulus	Hypothalamus Raphe nuclei
Spinoreticular	Lamina I, V-VIII	Anterolateral quadrant	Lat. reticular nuc Nuc. Ret gigantocell Medial medullary RF	Motivational, affective, responses Autonomic aspects	Medial thalamus Intralaminar thalamic nuclei Spinal cord via DLF
Spinocervical	Lamina III, IV	Dorsolateral cord	Lat. cervical nucleus	Alerting, orientation toward stimulus	Sup. colliculus
Dorsal column/ medial lemniscal	III, IV	Dorsal columns	Gracile/cuneate nuclei then to lateral thalamus	Unknown	Thalamic nuclei

(from: Robinson AJ. Central nervous system pathways for pain transmission and pain control. J Hand Ther 10:64-77, 1997)

The **perception** of sensory informations occurs in:

- *rostroventromedial medulla*: an important region for the integration and processing of ascending nociceptive information and modulation of descending output from the brain. This region contains excitatory and inhibitory cells that either facilitate or inhibit nociceptive reflexes and nociresponsive behaviours;
- *thalamus*: integrates and relays information to the somatosensory cortex, which in turn projects to adjacent cortical association areas, such as the limbic system;
- *limbic system:* includes the cingulate gyrus (involved with behaviour and emotion), amygdala (conditioned fear and anxiety), hippocampus (memory), hypothalamus (sympathetic autonomic activity), locus

coeruleus (arousal, vigilance, behaviour), and portions of the periaqueductal gray matter (fight or flight response, stress-induced analgesia);

- *somatosensory cortex*.[3]

Afferent nerve input, both somatic and autonomic, from an area of trauma or injury, activates hypothalamic–pituitary axis and sympathetic nervous system. There is a failure of the normal feedback mechanisms of hormone secretion control that causes immunological and haematological changes. There is generally release of catabolic hormones such as the catecholamines and pituitary hormones whereas anabolic hormones such as insulin and testosterone are suppressed. [7]

Changes occurring during the stress response

Physiological	Hormonal
	Metabolic
	Immunological
	Haematological
Psychological	Malaise (fatigue)
Behavioural	Reluctance to move

(from: Burton D, Nicholson G, Hall G. Endocrine and metabolic response to surgery. In Continuing Education in Anaesthesia, Critical Care & Pain | Volume 4 Number 5, 2004: 144-147)

1) Sympathetic nervous system:

Hypothalamic activation of the sympathetic nervous system causes an increased secretion of catecholamines from the adrenal medulla and release of norepinephrine from presynaptic nerve terminals. The increased of sympathetic activity acts on:

- *cardiovascular system,* with consequently tachycardia and hypertension
- *renal and adrenal gland functions*, with releasing of renin that causes the conversion of angiotensin I to angiotensin II; this stimulates the secretion of aldosterone from the adrenal cortex, which in turn increases sodium reabsorption from the distal convoluted tubule in the kidney;
- *pancreatic and hepatic functions:* with increasing in glucagon secretion, that stimulates the breakdown of glycogen in the liver and muscle leading to increased glucose and lactate concentrations as well as mobilization of free fatty acids (FFAs) from available lipid stores. [7,8]

2) Hypothalamic-pituitary-adrenal axis

- *Anterior pituitary:* under stimulation by hypothalamic releasing factors, the pituitary synthesizes pro-opiomelanocortin, that can be metabolized within the pituitary into ACTH (adrenocorticotrophic hormone), β-endorphin and an N-terminal precursor.

  The ACTH stimulates the adrenal cortical secretion of glucocorticoids with consequently increasing of circulating concentration of cortisol. Surgical stimulus also increases the GH (growth hormone or somatotrophin) and PRL (prolactin) secretion. GH stimulates protein synthesis and inhibits protein breakdown, promotes lipolysis and has an anti-insulin effect, with inhibition of glucose uptake and use by cells, which spares glucose for its use by neurons in situation of glucose scarcity; GH may also stimulate glycogenolysis in the liver. Concentrations of TSH, FSH and LH remain unchanged.
- *Posterior pituitary:* produces the ADH (antidiuretic hormone) and also stimulates, with corticotrophin-releasing factor, the secretion of pro-opiomelanocortin from the anterior pituitary. ADH is an important vasopressor and enhances haemostasis; ACTH release is enhanced by ADH.
- *Adrenal cortex:* cortisol secretion from adrenal cortex increases rapidly following the start of surgery; the cortisol response can be modified by anaesthetic intervention. Usually, the increased concentrations of circulating cortisol inhibit further secretion of ACTH, but this control is not effective after surgery, so the concentrations of both hormones remain high. Cortisol promotes proteolysis, lipolysis and gluconeogenesis; it inhibits glucose use by cells, so that blood glucose concentrations are increased. Cortisol has also an anti-inflammatory activity, with the inhibition of accumulation of macrophages and neutrophils into areas of inflammation and can interfere with the synthesis of inflammatory mediators, above all the prostaglandins.

- *Pancreas:* in response to trauma, the failure of the body to secrete insulin is partly caused by the inhibition of the β-cells in the pancreas by the a2-adrenergic inhibitory effects of catecholamines. Thus, the perioperative period is characterized by a state of functional insulin deficiency. In contrast to insulin, glucagon release promotes hepatic glycogenolysis and gluconeogenesis, but insulin effects predominate. Glucagon secretion increases briefly during surgery but it is not thought to make a major contribution to the hyperglycaemia.
- *Thyroid:* thyroids hormones stimulate oxygen consumption in many organs, increase the metabolic rate and heat production. Their circulating concentrations are inversely correlated with sympathetic activity and after surgery there is a reduction in thyroid hormone production, which returns to normal over a few day.[7,8]

Hormonal changes during surgery

Endocrine glands	Hormones	Change in secretion
Anterior pituitary	ACTH	Increases
	GH	Increases
	PRL	Increases
	TSH	May Increase or decrease
	FSH/LH	May Increase or decrease
Posterior pituitary	ADH	Increases
Adrenal cortex	Cortisol	Increases
	Aldosterone	Increases
Pancreas	Insulin	Often decreases
	Glucagon	Usually small increases
Thyroid	Thyroxine Tri- iodothyronine	Decreases

(From: J. P. Desborough. The stress response to trauma and surgery. *BJA: British Journal of Anaesthesia*, Volume 85, Issue 1, 1 July 2000, Pages 109–117)

ACTH: adrenocorticotrophic hormone; GH: growth hormone; PRL: prolactin; TSH: thyroid-stimulating hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; ADH: arginine vasopressin or antidiuretic hormone

3) Metabolic consequences of the endocrine response:

Consist in the increasing of catabolic process:

- *carbohydrate metabolism:* hyperglycaemia is a major feature of the metabolic response to surgery and results from an increase in glucose production and a reduction in glucose utilization. This is facilitated by catecholamines and cortisol, which promote glycogenolysis and gluconeogenesis. The mechanisms, which regulate glucose homeostasis, are ineffective because of initial failure of insulin secretion followed by insulin resistance. Potential risks of prolonged perioperative hyperglycemia include wound infection and impaired wound healing. There is also an increased risk of ischemic damage to the nervous system and myocardium.
- *protein metabolism:* initially there is inhibition of protein anabolism, followed later, if the stress response is severe, by enhanced catabolism, stimulated by increased cortisol and cytokine concentrations. The amino-acids, derived from catabolism, form new proteins in the liver known as acute phase proteins, but albumin production is reduced interfering with the maintenance of the extracellular volume. The liver also converts amino-acids into other substrates as glucose, fatty acids or ketone bodies. The loss of protein can be measured indirectly by increased nitrogen excretion (urea) in the urine.
- *lipid metabolism:* increased catecholamine, cortisol and glucagon secretion, in combination with insulin deficiency, promotes lipolysis and ketone body production. Triglycerids are converted by lipolysis to fatty acids and glycerol, and this latter become the substrate for gluconeogenesis; fatty acids may be oxidized and converted to ketone bodies or re-esterified.
- *salt and water metabolism:* Arginine vasopressin secretion results in water retention, concentrated urine, and potassium loss and may continue for 3–5 days after surgery. Renin is secreted from the juxtaglomerular cells of the kidney secondary to sympathetic efferent activation. It

converts angiotensin to angiotensin II, which in turn releases aldosterone from the adrenal cortex promoting sodium and water retention from the distal convoluted tubule. [7,8]

4) Immunological and haematological changes:

The immune system and neuroendocrine system are closely related. In response to tissue injury from surgery or trauma, cytokines are synthesized by activated macrophages, fibroblasts, endothelial and glial cells. Cytokines are low molecular weight, heterogeneous glycoproteins that include interleukins (IL) 1–17, interferons, and tumour necrosis factor. Although they exert most of their effects locally (paracrine), they can also act systemically (endocrine). Cytokines play an important role in mediating immunity and inflammation by acting on surface receptors of target cells. The most important cytokine associated with surgery is IL-6 and peak circulating values are found 12–24 h after surgery. The size of IL-6 response reflects the degree of tissue damage which has occurred. IL-6, and other cytokines, cause the acute phase response, which includes the production of acute phase proteins such as fibrinogen, C reactive protein, complement proteins, a2-macroglobulin, amyloid A and ceruloplasmin. Other effects of cytokines include fever, granulocytosis, haemostasis, tissue damage limitation and promotion of healing. Cytokines may increase the release of cortisol and this latter limits their production via a negative feedback system. Thus, the cortisol response to surgery limits the severity of the inflammatory response. [7]

2. Veterinary pain evaluation

Differences in pain tolerance have been demonstrated experimentally in people and animals and these play an important role in pain management; in fact, it is important

to know that there are individuals with a lower threshold for pain and others with particularly stoic nature, that may be sex-related [9,10], age-related [10,11] or breed-related. [12,13]

The American College of Veterinary Anaesthesiologists (ACVA) in the 2006 has written a position paper where it said that "animal pain and suffering are clinically important conditions that adversely affect an animal's quality of life, either in the short or long term". It also said that "an important part of determining whether an animal is in pain is the ability to recognize departures from normal behaviour and appearance of that animal". In this paper a list of behavioural changes to be considered for the evaluation of the presence or absence of pain in an animal is drawn up:

- Changes in personality or attitude. A normally quiet and docile animal becomes suddenly aggressive, or an aggressive animal becomes quiet. An animal may attempt to bite, especially when a painful area is palpated. The animal may not interact with the clinician in a normal manner, but may seem to be unresponsive or withdrawn.
- Abnormal vocalization, especially when a painful area is palpated or the animal is forced to move. For example, dogs whine or whimper, cats hiss or growl, pigs grunt and squeal excessively, primates grunt or scream, rats squeak at an unusual pitch, mice chatter. Vocalization tends to be an insensitive and nonspecific indicator of pain and should not be relied on as the sole criterion for determining whether an animal requires treatment for pain.
- Licking, biting, scratching or shaking of a painful area. If excessive, these behaviours can lead to self-mutilation.
- Changes in the appearance of the haircoat. Ruffled fur, a greasy appearance indicative of a lack of grooming, and piloerection may be indicative of pain.
- Changes in posture or ambulation. Limping or carrying of a painful appendage; tensing of abdominal and back muscles to produce a tucked up appearance is especially noticeable in dogs, cats, and rodents.

- Changes in activity level. An animal may become restless and pace or repetitively lie down, get up, and lie down again. In contrast, an animal may be recumbent and lethargic or reluctant to move with guarding of the painful area.
- Changes in appetite, such as a decrease in food and water consumption leading to weight loss and dehydration.
- Changes in facial expression. Eyes become dull and pupils may be dilated. Pinning of the ears, grimacing, and a sleepy or photophobic appearance may be evident.
- Excessive sweating or salivation. Horses frequently sweat in response to pain; however, cattle do not. Stressed rodents often salivate excessively.
- Oculonasal discharge. Rats when stressed often shed porphyrin pigment in their tears and appear to be bleeding from their eyes and nose.
- Teeth grinding is frequently heard in rabbits, cattle, sheep, and goats experiencing pain.
- Changes in bowel movements or urination, such as diarrhea with soiling of the perineum, dysuria, and tenesmus.

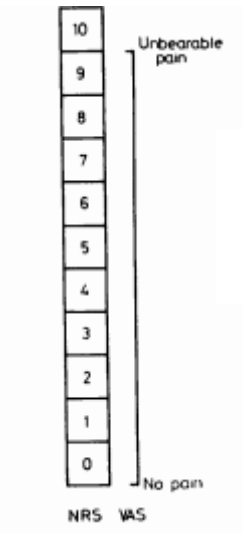
Other parameters that are indicative of pain include increasing in heart rate, respiratory rate, arterial pressure and body temperature. Blood samples can be evaluated for elevations in glucose, corticosteroid, and catecholamine concentrations.[14]

The detection of pain is one of the most challenging problems in veterinary medicine. In people, the self-reporting of pain is the gold standard for the assessment of pain; in veterinary medicine, the recognition of pain is based on the interpretation of animal's behaviour and cardiovascular variations by the veterinary surgeon/nurse in the case of acute pain and by the owner in the case of chronic pain.[15, 16]

Before analgesic drugs can be administered to reduce pain, the signs of pain must be assessed quantitatively, with using pain scales.

In the past the scales used to assess pain in animals and human beings have been based on assessments of its intensity alone, the so-called unidimensional scales, as:

- Simple Descriptive Scale (SDS), which uses 4 or 5 points based on verbal description (nil, mild, moderate, severe, very severe). The use of this scale for comparative purposes is limited by its lack of sensitivity for detecting relatively small changes.
- Numerical Rating Scale (NRS), marked 0-10 or 0-20
- Visual Analogue Scale (VAS), utilises a straight line, conventionally 10 cm long, whose extreme limits are marked by perpendicular lines. At the ends of the scale there is a verbal description of each extreme of the symptom to be evaluated. [17]



Formats of the numerical rating (NRS) and visual analogue (VAS) scales

(*from: Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA.* ***Studies with pain rating scales****.Ann Rheum Dis. 1978 Aug;37(4):378-81*)

These scales have been shown to be unreliable in the assessment of pain in patients who cannot communicate, for example patients suffering of dementia, children and animals.

This limitation led to the development of multidimensional scales. *Melzack and Torgerson* (1971) developed a 'language of pain', which considered other qualities of pain in addition to its intensity, based on the interpretation of behaviours such as facial expressions, postures and activities. This language formed the basis of the McGill pain questionnaire (Melzack 1975) which was designed to provide quantitative assessments of clinical pain that could be treated statistically.

It is only recently that the utility of such methods has been recognised by veterinarians.

- *Morton and Griffiths* (1985) first proposed a composite scale for assessing pain in animals, in the form of 'Guidelines for the recognition of pain, distress, and discomfort in experimental animals and a hypothesis for assessment'. They suggested that specific behaviours, including posture, vocalisation, temperament, food and water intake and locomotion might be used as indicators of pain. Scores from 0 to 3 were allocated for specific changes in eight characteristics, including the animal's bodyweight, its appearance, any relevant clinical signs, unprovoked behaviour and responses to stimuli. The total pain score was the sum of these scores and could range from 0 to 24. They also defined what interpretations should be applied to certain ranges of total scores; 0 to 4 was regarded as normal; 5 to 9 the animal should be monitored carefully; 10 to 14 the animal should be treated with analgesics or euthanased, or the experiment should be terminated. They did not distinguish between species. The guidelines were designed to ensure that practice was consistent between laboratories and to provide an objective set of criteria for safeguarding animals' welfare. No criteria for the development of the guidelines were provided, and it is therefore questionable whether they can do more than ensure consistent practice between laboratories.
- *Sanford and al.* (1986) published further 'Guidelines for the recognition and assessment of pain in animals'. Their aim was to provide an effective and uniform set of criteria for controlling the severity of the pain. The behaviours associated with pain were the animal’s posture, facial expression, gait, acceptance of handling, vocalisation and overall mental status. These guidelines also suggested that a clinical examination should be carried out, paying particular attention to physiological signs such as pupil dilation, and changes in blood pressure, heart rate and body temperature. No rationale for the selection of these criteria was provided and the properties of the measurements made were not explored.

- *Conzemius and others* (1997) described a 'Numerical Rating Scale' for assessing postoperative pain in dogs, which differs from the NRS mentioned previously. The method scores three types of behaviour, vocalisation, movement and agitation, scores of 0 to 2 being allocated to the first two behaviours and 0 to 3 for the third, according to predefined rules, giving a possible total score of between 0 and 7. This numerical scale provided defined criteria for the assessment of different aspects of the animals' behaviour, but the authors did not provide selection criteria for the types of behaviour or describe how the weights were attributed to them. No results of the use of this scale have been reported and it is therefore not possible to assess its consistency or value.
- The *Colorado State University Veterinary Teaching Hospital Pain Score* (Hellyer and Gaynor 1998) is a scale for the assessment of pain in cats and dogs which is based on eight categories of behaviour and physiological signs considered to be indicative of pain: comfort, movement, appearance, unprovoked behaviour, interactive behaviour, vocalisation, heart rate and respiratory rate. Each category is assigned a score of between 0 and 4 according to predefined criteria, the total score being the total of the scores for each category. The aim of this scale was to estimate an animal's requirement for analgesia. However, no details were given of how the categories were selected for the scale, and its validity in the assessment of pain is therefore uncertain.
- The *University of Melbourne Pain Scale* (UMPS) (Firth and Haldane 1999) evaluates postoperative pain in dogs on the basis of assessments of behaviour and physiological signs. It is composed of six categories: physiological variables, response to palpation, activity, mental status, posture and vocalisation. The method was similar to that used in the development of the Children's Hospital of Eastern Ontario Pain Scale (McGrath and others 1985), a behaviour-based scale for the assessment of pain in children. The assessments of the animal's mental status, heart rate and respiratory rate were based on the change from its presurgery status,

so this scale is limited to be used in dogs undergoing surgery. Ranges are defined for the increases in heart and respiratory rates and scores are consequently assigned, assuming that there is a direct relationship between the changes in physiological signs and the intensity of pain, although the converse has been demonstrated.

- The *Glasgow coma scale* (GCS) (Teasdale and Jennett 1974) concentrates on three aspects of behavioural response, and its universality depends on identifying responses which can be clearly defined and accurately graded according to degree of dysfunction. This scale must be practical to use in many different places by staff without special training. It was therefore considered important to define the behavioural descriptors precisely, so that the observer was in no doubt as to their interpretation.
- The *Glasgow Composite Measure Pain Scale*, developed by Holton and other (2001), is a pain scale in dogs which might be used by everyone, that provides clear definitions of all the expressions used. It is based on the McGill pain questionnaire, in which pain descriptors are supplied by practising veterinary surgeons familiar with the behavioural signs of acute pain in dogs. After refinement, the final list of descriptors was divided into seven categories: posture, comfort, vocalisation, demeanour, mobility, attention to wound and response to touch. Many of the behaviours and signs of the other behaviour-based scales for the assessment of pain in dogs were included, such as the Colorado State University scale that includes vocalisation, movement, unprovoked and interactive behaviour, and heart rate and respiratory rate; mobility and vocalisation are included in the guidelines for pain recognition defined by Morton and Griffiths (1985); Firth and Haldane (1999) included activity, posture and vocalisation in their scale; Potthoff and Carithers (1989) included other indicators of pain which have been used in the present scale, such as body movement, restlessness, panting and whimpering. The Glasgow scale is a validated pain scale, for the strong agreement with past literature and for the fact that the pain descriptors included in this scale

are considered to be strictly associated with pain by wider veterinary community.[18]

Morton and al. (2005) have established an interval level measurement for assessment of acute pain in dogs and to investigate the validity of the scale.[19]

TABLE 5: Questionnaire used to assess a dog's score on the Glasgow scale for assessing pain

The questionnaire is made up of a number of sections each of which have several possible answers. Please tick the answers that you feel are appropriate to the dog you are assessing. If more than one answer is appropriate then tick all that apply. Approach the kennel, ensure you are not wearing a laboratory coat or theatre 'greens' as the dog may associate these with stress and/or pain. While you approach the kennel look at the dog's behaviour and reactions. From outside the dog's kennel look at the dog's behaviour and answer the following questions.

Look at the dog's posture, does it seem . . .
- Rigid ☐
- Hunched or tense ☐
- Neither of these ☐

Does the dog seem to be . . .
- Restless ☐
- Comfortable ☐

If the dog is vocalising is it . . .
- Crying or whimpering ☐
- Groaning ☐
- Screaming ☐
- Not vocalising/none of these ☐

If the dog is paying attention to its wound is it . . .
- Chewing ☐
- Licking or looking or rubbing ☐
- Ignoring its wound ☐

Now approach the kennel door and call the dog's name. Then open the door and encourage the dog to come to you. From the dog's reaction to you and its behaviour when you were watching it assess its character.

Does the dog seem to be . . .
- Aggressive ☐
- Depressed ☐
- Disinterested ☐
- Nervous or anxious or fearful ☐
- Quiet or indifferent ☐
- Happy and content ☐
- Happy and bouncy ☐

Now look at the dog's response to stimuli. If the mobility assessment is possible then open the kennel and put a lead on the dog. If the animal is sitting down encourage it to stand and then come out of the kennel. Walk slowly up and down the area outside the kennel. If the dog was standing up in the kennel and has undergone a procedure which may be painful in the perianal area, ask the animal to sit down.

During this procedure did the dog seem to be . . .
- Stiff ☐
- Slow or reluctant to rise or sit ☐
- Lame ☐
- None of these ☐
- Assessment not carried out ☐

The next procedure is to assess the dog's response to touch. If the animal has a wound, apply gentle pressure to the wound using two fingers in an area approximately 2 inches around it. If the wound is impossible to touch, then apply the pressure to the closest point to the wound. If there is no wound then apply the same pressure to the stifle and surrounding area.

When touched did the dog . . .
- Cry ☐
- Flinch ☐
- Snap ☐
- Growl or guard wound ☐
- None of these ☐

(from: *Holton L, Reid J, Scott EM, Pawson P, Nolan A. Development of behaviour-based scale to measure acute pain in dogs. Vet Rec 148:525-531,2001)*

TABLE 6: Definitions of the expressions used in the Glasgow scale for assessing pain in dogs

Category	Definition
Posture	Rigid: Animal lying in lateral recumbency, legs extended or partially extended in a fixed position Hunched: When animal is standing, its back forms a convex shape with abdomen tucked up, or, back in a concave shape with shoulders and front legs lower than hips Tense: Animal appears frightened or reluctant to move, overall impression of tight muscles; animal can be in any body position Normal body posture: Animal may be in any position, appears comfortable, muscles relaxed
Activity	Restless: Moving bodily position, circling, pacing, shifting body parts, unsettled Comfortable: Animal resting and relaxed, no avoidance or abnormal body position evident, or settled, remains in same body position, at ease
Vocalisation	Crying: Extension of the whimpering noise, louder and with open mouth Whimpering: Often quiet, short, high pitched sound, frequently closed mouth (whining) Groaning: Low moaning or grunting deep sound, intermittent Screaming: Animal making a continual high pitched noise, inconsolable, mouth wide open
Attention to wound area	Chewing: Using mouth and teeth on wound area, pulling stitches Licking: Using tongue to stroke area of wound Looking: Turning head in direction of area of wound Rubbing: Using paw or kennel floor etc to stroke wound area Ignoring: Paying no attention to wound area
Demeanour	Aggressive: Mouth open or lip curled showing teeth, snarling, growling, snapping or barking Depressed: Dull demeanour, not responsive, shows reluctance to interact Disinterested: Cannot be stimulated to wag tail or interact with observer Nervous: Eyes in continual movement, often head and body movement, jumpy Anxious: Worried expression, eyes wide with white showing, wrinkled forehead Fearful: Cowering away, guarding body and head Quiet: Sitting or lying still, no noise, will look when spoken to, but not respond Indifferent: Not responsive to surroundings or observer Content: Interested in surroundings, has positive interaction with observer, responsive and alert Bouncy: Tail wagging, jumping in kennel often vocalising with a happy and excited noise
Mobility	Stiff: Stilted gait, slow to rise or sit, may be reluctant to move Slow to rise or sit: Slow to get up or sit down but not stilted in movement Reluctant to rise or sit: Needs encouragement to get up or sit down Lame: Irregular gait, uneven weight bearing when walking Normal mobility: Gets up and lies down with no alteration from normal
Response to touch	Cry: A short vocal response; looks at area and opens mouth, emits a brief sound Flinch: Painful area is quickly moved away from stimulus either before or in response to touch Snap: Tries to bite observer before or in response to touch Growl: Emits a low prolonged warning sound before or in response to touch Guard: Pulls painful area away from stimulus or tenses local muscles in order to protect from stimulus None: Accepts firm pressure on wound with no reaction

(from: *Holton L, Reid J, Scott EM, Pawson P, Nolan A. Development of behaviour-based scale to measure acute pain in dogs. Vet Rec 148:525-531,2001)*

- *The Short-Form of Glasgow Composite Measure Pain Scale (CMPS-SF),* developed by Reid and other (2007), derived from previous scale, in order to have a easy and fast way for routine clinical use. It is comprises six behavioural categories with associated descriptive expressions (items): vocalisation, attention to wound, mobility, response to touch, demeanour and posture/activity. Four of the six categories contain five items, one contains four and the other six. The observer chooses the single item within each category which best fits the dog's condition and the pain score is the sum of the rank scores of each item chosen. The maximum score for the six categories is 24, or 20 if mobility is impossible to assess. The clinical decision-point for analgesic intervention, when mobility could be assessed, is established with a level as 6/24 and higher; while analgesic intervention is gave with a level of 5/20 and higher, if section B could not be carried out as a result of the animal's physical condition, and consequently total score was out of 20 rather than 24.[20]

  Murrell et al. (2008) have applied this scale in a centre with a different surgical procedures and analgesic protocols, and where English is not the first language, to test its validity in a different clinical environment. The modified scale was used to score pain in 60 dogs during the 24 hours after surgery. They have demonstrated that the modified CMPS is a useful scale for measuring perioperative pain in a clinical setting, where a wide variety of analgesic and anaesthetic protocols are used. [20]

SHORT FORM OF THE GLASGOW COMPOSITE PAIN SCALE

Dog's name _____

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

Surgery Yes/No (delete as appropriate)

Procedure or Condition_____

_____

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

A. Look at dog in Kennel

Is the dog?

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

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

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

When the dog rises/walks is it?

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

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

Does it?

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

D. Overall

Is the dog? *(v)*		*Is the dog?* *(vi)*	
Happy and content or happy and bouncy	0	Comfortable	0
Quiet	1	Unsettled	1
Indifferent or non-responsive to surroundings	2	Restless	2
Nervous or anxious or fearful	3	Hunched or tense	3
Depressed or non-responsive to stimulation	4	Rigid	4

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

(from: *Reid J, Nolan AM, Hughes JML, Lascelles D, Pawson P, Scott EM.* ***Development of the short-form Glasgow Composite Measure Pain Scale (CMPS-SF) and derivation of an analgesic intervention score.*** *Animal Welfare 2007, 16(S): 97-104)*

Beyond humanitarian consideration pain can induce catabolism, impair respiration, delay wound healing, prolong periods of hospitalization, and increase morbidity and mortality. [21]

In these latter years, many surveys have been conducted to obtain information related to attitudes, opinions and knowledge of both veterinary surgeons and pet's owners, about acute and chronic pain and the use of analgesic drugs in small animal veterinary practice. [22-27]

It seems there is a positive trend about the importance of providing effective pain management for small animals by the veterinary professionists, but peri-operative use of analgesic drugs is still suboptimal.[15]

Owners believed more frequently that analgesics are always needed for surgical procedures than for the medical conditions [26,27]; in fact difficulties with owner compliance is reported as one of the major barriers to adequate treatment of chronic pain, with difficulties of pain assessment and expense of drugs.[25]

Simon et al. conclude by saying that improving our understanding of pet owners' perceptions and knowledge of anaesthesia, surgery and pain can lead to better client education. [27]

3. Veterinary Pain management: systemic and local analgesia

The concept of preemptive analgesia is introduced for the first time by Crile [28], who observed that if pain transmission was blocked prior to the initial surgical incision, postoperative mortality was decreased as well as the intensity and duration of postoperative pain.

Preemptive analgesia is an antinociceptive therapy whose aim is to prevent both peripheral and central sensitization, in order to avoiding the postoperative amplification of pain sensation.

Treatment can be performed at the periphery, to block inputs along sensory axons, or at CNS sites using single or combinations of analgesic drugs, injected systemically, in the form of single shot or in continuous rate infusion (CRI). [28,29]

a) Opioids

Opioids are among the oldest and most frequently used drugs for the alleviation of pain. They have high efficacy and they are remarkably safe, with the benefit of reversibility, through the administration of naloxone, an opioid antagonist. These drugs bind to opioid receptors located in the central and peripheral nervous system and cause a conformational change that increases their affinity for guanine nucleotide binding proteins (G-coupled proteins). In the perioperative period, they are administered to produce analgesia and sedation as part of premedication (neuroleptanalgesia) and multimodal analgesic protocols.[30]

Side effects of μ-opioid receptor agonists are: depression tidal volume and gas exchange, diminution of breathing rate progressing to respiratory arrest with higher doses, decrease chest wall compliance, and increase upper airway resistance, for their action on discharges of respiratory bulbospinal, vagal, propriobulbar neurons and phrenic nerve activity. [31]

Opioids have been traditionally administered by the intravenous, intramuscular, subcutaneous route as single shot, or as intravenously constant rate infusions (CRI).

A recent alternative pharmaceutical form of opioid administration is the transdermal patch, such as fentanyl [32-34] and buprenorphine [35,37], or the transdermal solution of fentanyl [38], with the aim to extend their action duration and potentially mitigate the disadvantages of both oral and parenteral opioid administration.

Opioid drugs are also administered to enhance loco-regional anaesthesia, both alone or in co-administration with local anaesthetics. Morphine is a highly hydrophilic drugs that produces analgesia 30–40 min after epidural administration, with long duration of effect due to the delayed systemic absorption and longer maintenance in the spinal cord. Epidural or spinal administered opioids relieve somatic and visceral pain by selectively blocking nociceptive impulses without interfering with sensory and motor function or depressing the sympathetic nervous system.

Intra-articular administration of morphine has become increasingly popular after arthroscopy surgery; after joint inflammation, a significant increase in μ-opioid receptors in both articular and peri-articular tissues occurs. [30]

Table 2
Opioids used in the dog and cat

Type	Drug	Dosage for Dogs	Dosage for Cats	Notes
Full mu agonists	Morphine (Morphine)	0.05–0.1 mg/kg IV q 1–2 h 0.05–0.1 mg/kg/h IV CRI 0.5–1.0 mg/kg IM q 3–5 h 0.1 mg/kg epidural q 12–24 h	0.05–0.1 mg/kg IV q 1–2 h 0.05–0.1 mg/kg/h IV CRI 0.1–0.2 mg/kg IM q 3–4 h 0.1 mg/kg epidural q 12–24 h	Can produce dysphoria in cats with higher doses Histamine release when given IV
	Hydromorphone (Dilaudid)	0.05–0.1 mg/kg IV q 1–2 h 0.05–0.1 mg/kg/h IV CRI 0.1–0.2 mg/kg IM q 3–4 h	0.05–0.1 mg/kg IV q 1–2 h 0.01–0.05 mg/kg/h IV CRI 0.05–0.1 mg/kg IM q 3–4 h	Associated with occasional hyperthermia in cats No histamine release with IV administration Less emesis than morphine
	Oxymorphone (Numorphan)	0.05–0.1 mg/kg IV, IM q 4 h	0.05–0.1 mg/kg IV, IM q 4 h	—
	Fentanyl (Sublimaze)	0.01–0.04 mg/kg IM q 30 min 0.002–0.005 mg/kg IV 0.002–0.02 mg/kg/h IV CRI	0.005–0.02 mg/kg IM q 30 min 0.002–0.005 mg/kg IV 0.002–0.02 mg/kg/h IV CRI	—
	Fentanyl (Recuvyra)	2.7 mg/kg topical Duration is at least 96 h	Not approved	Approved for use in the dog Must be trained in application before using
	Remifentanil (Ultiva)	0.004–0.01 mg/kg IV 0.004–0.012 mg/kg/h IV CRI	0.004–0.006 mg/kg IV 0.004–0.006 mg/kg/h IV CRI	Constant rate infusion does not require a loading dose
	Methadone (Dolophine)	0.1–0.5 mg/kg IV, IM q 2–4 h	0.1–0.25 mg/kg IV, IM q 2–4 h 0.1–0.3 mg/kg OTM q 8–12 h	—
Partial mu agonist	Buprenorphine (Buprenex)	0.005–0.02 mg/kg IV, IM q 4–8 h	0.005–0.02 mg/kg IV, IM q 4–8 h 0.02–0.04 mg/kg OTM q 4–8 h	Onset of action may be 30 min or more
	Buprenorphine (Simbadol)	Not approved	0.24 mg/kg SC q 24 h	Administer 1 h before surgery Continue daily dosing for 3 d
Kappa agonist/mu antagonist	Butorphanol (Torbugesic)	0.2–0.4 mg/kg IV, IM q 1 h	0.2–0.4 mg/kg IV, IM q 1 h	—
Mixed mechanism mu agonists	Tramadol (Ultram)	1–4 mg/kg IV q 6–8 h	1–4 mg/kg IV q 6–8 h	—
	Tapentadol (Nucynta)	2–6 mg/kg IV	—	—

Abbreviations: CRI, constant rate infusion; IM, intramuscularly; IV, intravenously; OTM, oral transmucosal; SC, subcutaneously.

*(from: Berry SH. **Analgesia in the Perioperative Period.** Vet Clin North Am Small Anim Pract. 2015 Sep;45(5):1013-27. doi: 10.1016/j.cvsm.2015.04.007. Epub 2015 May 26)*

b) Local anaesthetics

Local anaesthetics are inexpensive, easy to use, and rarely associated with significant adverse events. They can be incorporated into a balanced analgesic plan in several ways and it is recommended that they be included in the plan of every surgical patient.

Local anaesthetics prevent the conduction and propagation of nerve impulses by binding to voltage-gated sodium channels, producing complete analgesia. Adverse events associated with local anaesthetic administration are usually the result of inadvertent intravenous administration (above all bupivacaine) or overdose. Signs of local anaesthetic toxicity include ataxia, nystagmus, and tremors, which can progress to convulsions, unconsciousness and respiratory arrest.

Cardiovascular manifestations of local anaesthetic toxicity include bradycardia and sinus arrest. The versatility of local anaesthetics allows them to be used in several ways:

- Topical: local anaesthetics may be applied to skin or mucosa to desensitize areas (eg, lidocaine spray, lidocaine patch);
- Infiltrative: local anaesthetics can be injected near specific nerves or placed in wounds (eg, peripheral nerve blocks, soaker catheters);
- Systemic: lidocaine may be given intravenously, in continuous rate infusion, in order to decrease inhaled anaesthetic requirements and provide anti-inflammatory, antiarrhythmic and analgesic effects;
- Neuraxial: intrathecal or epidural application of local anaesthetics. [39]

Table 4
Local anesthetics used for the treatment of acute pain in the dog and cat

Drug	Onset	Duration	Dosage in the Dog	Dosage in the Cat
Lidocaine (Lidocaine)	5–10 min	1–3 h	2 mg/kg IV 0.025–0.05 mg/kg/min IV CRI 4.4 mg/kg epidural Maximum recommended dose: 8 mg/kg	Constant rate infusion not recommended in the cat[52] 4.4 mg/kg epidural Maximum recommended dose: 6 mg/kg
Mepivacaine (Carbocaine V)	3–10 min	2–4 h	Maximum recommended dose: 4.5 mg/kg	Maximum recommended dose: 3 mg/kg
Bupivacaine (Marcaine)	10–20 min	3–6 h	1–1.5 mg/kg epidural Maximum recommended dose: 2 mg/kg	1 mg/kg epidural Maximum recommended dose: 1 mg/kg
Etidocaine (Duranest)	3–5 min	5–10 h	Maximum recommended dose: 8 mg/kg	Maximum recommended dose: 4 mg/kg
Ropivicaine (Naropin)	15–20 min	1.5–6 h	0.5 mg/kg epidural Maximum recommended dose: 3 mg/kg	0.5 mg/kg epidural Maximum recommended dose: 1.5 mg/kg

*(from: Berry SH[1]. **Analgesia in the Perioperative Period.** Vet Clin North Am Small Anim Pract. 2015 Sep;45(5):1013-27. doi: 10.1016/j.cvsm.2015.04.007. Epub 2015 May 26)*

c) Non-steroidal anti-inflammatory drugs (NSAIDs)

The anti-inflammatory and analgesic properties of the NSAIDs are mediated by the inhibition of COX-1 and COX-2, responsible of inflammatory mediators production of interest in nociception, such as the prostaglandins, thromoboxane A2 and prostacyclins. NSAIDs are useful in both acute and chronic pain management, particularly osteoarthritis. (40)

d) Ketamine

Ketamine is a dissociative agent with NMDA receptor antagonism and sympathomimetic effects. At low doses it provides analgesia, while also providing anaesthesia at high dose. It is thought to provide less intense analgesia than pure-μ opioids and is often used in combination with an opioid for multimodal analgesic effects. (41)

In one study of 2000, Slingsby&Waterman-Pearson said that the use of ketamine in dogs undergoing ovariohysterectomy as pre-emptive analgesia has required less analgesic intervention than the control group that were not treated with ketamine; this latter did not require significantly more analgesic intervention than the treated with ketamine at extubation, suggesting that preoperative ketamine treatment give some benefit over administration of ketamine post-operatively. (42)

Ketamine can also been used in continuous rate infusion, with a significant sparing effect on the MAC of isoflurane in dogs. (43) Kaka et al have reported in their study of 2016 that the minimum serum concentration of ketamine to produce analgesia in dogs is between 100-200 ng/mL during infusion. (44)

e) α2-agonist:

Alpha2-adrenoreceptor agonists are widely used in small animal for their potent sedative and analgesic properties, and for the possibility to reverse their action, in those cases where side effects occur. The administration of an α_2-antagonist (atipamezole) reverses side effects, but also sedation and analgesia provided by these drugs. This class of drugs have significant effects on the cardiovascular and respiratory systems:

- Cardiovascular effects include: bradycardia, hypertension, hypotension, reduction in cardiac output and stroke volume.
- Respiratory effects include: reduction in respiratory rate and tidal volume, which may result in respiratory acidosis and hypoxemia in some animals.

These effects can be seen even when very small doses of α2-agonists are administered, so their use should be limited to those animals that can tolerate cardiovascular and respiratory systems imbalance.

In premedication, their administration with opioids can act synergistically, enhancing analgesia and sedation and reducing the doses used of each drug. In post-operative period, small doses can provide sedation and analgesia especially in animals experiencing dysphoria.

The α2-agonists may be used as adjuvant to local anaesthetics in peripheral nerve blocks, prolonging their duration. Intra-articular injections of α2-agonists also may be beneficial, as shown by studies involving humans undergoing arthroscopy and rats suffering from arthritic pain. [45]

Dexmetomidine may be used in continuous rate infusion (CRI), alone or in combination with other drugs (eg lidocaine, fentanil) to reduce halogenated agents MAC (minimum alveolar concentration) during anaesthesia period [46,47] or to improve analgesia in perioperative period. [48, 49]

f) other drugs:

- Gabapentin is a non-opioid medication, structurally similar of γ-amino butyric acid, which has commonly used as an anticonvulsant and antinociceptive drug, throughby the release of some neurotransmitters, such as substance P and glutamate, and interacting with γ-aminobutyric acid receptors in the spinal cord. It was found that its administration with opioids in perioperative period may enhance sedation and analgesia, and reduce post-operative analgesic requirements. [39,50,51]
- Maropitant: is an NK-1 receptor antagonist approved for use as an antiemetic zone for dogs and cats for its central action in the chemoreceptor trigger. In one study, Alvillar et al (2012) found that the intravenously, but not epidural, administration of maropitant reduce sevofluorane MAC. [52]

  In another study, Marquez et al (2015) compared the use of maropitant (1 mg/kg SQ) and morphine (0,5 mg/kg SQ) as premedication in dogs undergoing ovariohysterectomy; they no found major clinical difference between groups; suggesting that maropitant given as a pre-anaesthetic may be comparable to 0.5 mg/kg of morphine for an OHE and may improve the post-operative recovery. [53]

  However, its analgesic role is still controversial and further studies are needed.

4. Loco-regional analgesia

Peripheral nerve blocks are becoming increasingly popular for perioperative use as analgesic techniques in small animals.

The influence of regional anaesthesia on the stress response has been extensively investigated. In a recent study of 2016, Romano et al. have measured the stress biomarkers (glycaemia and cortisol release), postoperative pain and recovery quality in dogs undergoing stifle surgery, in order to compare two loco-regional techniques (peripheral femoral and sciatic nerve block; spinal anaesthesia), pre-operatively performed, with peri-operative systemic fentanil and post-operatively methadone. They found that analgesia with a peripheral nerve block or spinal anaesthesia prevented the glycaemic and cortisol responses to surgery, promoted better recovery quality, and decreased postoperative pain scores compared with fentanil, so regional anaesthesia techniques were found to be excellent alternatives to fentanyl administration.

There are many studies, both in human and in animals, that widely show the advantages of using one analgesia loco-regional technique instead of systemic analgesia, or a combination between both, in order to reduce systemic opioid administration and to avoid their side effects such as bradycardia, hypotension, hypoventilation, ileus, nausea, vomiting and dysphoria. [31,54]

The table below is a list of loco-regional anaesthesia techniques, but further papers that study the use of various methods of neuro-localization, such as electroneurostimulation and ultrasound, are frequently published.

Table 5
Common methods to incorporate local anesthetics into analgesic protocols

Area of Body Effected	Local Anesthetic Technique
Head	Selective nerve blocks (eg, inferior alveolar, maxillary)
Forelimb	Paravertebral forelimb block Brachial plexus block Proximal RUMM block Distal RUM Intravenous regional anesthesia
Thorax	Intercostal nerve blocks Intrapleural injection Epidural injection
Abdomen	Transverse abdominis plane block[53] Epidural injection Intrapleural injection
Hind limb	Selective nerve blocks (eg, femoral) Epidural injection
Testicle/ovary	Intratesticular injection Infiltration of ovarian ligament
Wounds/incisions	Infiltration Diffusion catheter[54] Transdermal patch
Joints	Intra-articular injection

Abbreviations: RUM, radial, ulnar, median; RUMM, radial, ulnar, musculocutaneous, and median nerves.

*(from: Berry SH[1]. **Analgesia in the Perioperative Period.** Vet Clin North Am Small Anim Pract. 2015 Sep;45(5):1013-27. doi: 10.1016/j.cvsm.2015.04.007. Epub 2015 May 26)*

Materials and methods

The study was conducted in the period between April 2017 and April 2018, in the Centre Hospitalier Universitaire of the École Nationale Vétérinaire d'Alfort (ENVA), Maisons-Alfort, France. This study was approved, according to Directive 2010/63/EU, by the Chair of the Veterinary University Hospital Ethics Approval Board, and informed consent was obtained from all owners.

Objective

The aim of this study is to compare motor and sensitive block duration, quality of anaesthesia and analgesia after sciatic/femoral electrolocation nerve block with bupivacaine alone and in combination with dexmedetomidine in dogs undergoing unilateral stifle joint surgery.

Our hypothesis was that perineural dexmedetomidine combined with bupivacaine might offer a longer duration of sensory block than bupivacaine alone and consequently a better analgesia quality, and we could reduce the dose of bupivacaine avoiding supplemental opioid administration.

Study design

Prospective, randomized, double blinded clinical trial

Animals

Thirty-one dogs, median age 4,4 years (1 – 11) and median weight 25,2 kg (3 - 68), undergoing unilateral stifle joint surgery, assessed to be ASA physical status I or II after physical examination and haematology and serum chemical analyses were enrolled in this study.

The population included both male and female dogs (15 and 16 respectively), of various breeds: : 3 Labrador Retrievers, 3 Mixed-unknown, 3 Yorkshire Terriers, 3 Majorca Mastiff Dogs, 2 Golden Retrievers, 2 American Bull Dogs and 1 each of American Staffordshire Terrier, Bernese Mountain Dog, Bulldog, Canarian Dog, Cesky Fousek, Chihuahua, Continental Bulldog, Creole Dog, Dachshund, Doberman Pinscher, Dogo Argentino, Eurasier, German Shepherd Dog, Great Pyrenees, Pitt Bull cross.

Procedure study

Surgery procedures included:

- Tibial plateau leveling osteotomy (TPLO);
- Trochleoplasty;
- Tibial Tuberosity Transposition;
- Transarticular Stabilization.

In particular: 21 dogs are presented for Tibial Plateau Levelling Ostectomy, 5 Transarticular Stabilization of cruciate ligament rupture, 2 Tibial Tuberosity Transposition, 1 Trochleoplasty, 1 Trochleoplasty + Tibial Tuberosity Transposition, 1 Tibial Plateau Levelling Ostectomy + Trochleoplasty.

All the dogs received a standard general anaesthesia protocol:

- premedication was performed with intramuscularly acepromazine 0,03 $mgkg^{-1}$ (Calmivet® ; Vetoquinol, France);
- after twenty minutes, a catheter was aseptically placed in a cephalic vein, and all dogs received intravenously propofol to effect (~ $4mgkg^{-1}$, Propovet; Zoetis, France) and midazolam 0,2 $mgkg^{-1}$ (Midazolam; Mylan, France), as induction
- after orotracheal intubation, anaesthesia was maintained with isoflurane in oxygen diluted. The end-tidal isoflurane (EtISO) was titrated to lowest percentage able to maintain a suitable plane of anaesthesia (between 0.9% and 1.4%).

Lactated Ringer's solution was administered intravenously at 5 $mLkg^{-1}h^{-1}$ throughout the anaesthesia period and in the early post-anaesthesia recovery.

Prior to each block, hair over each target site was clipped and the skin was aseptically prepared for injection.

Dogs were randomly allocated to three treatments:

- Group A (10 subjects) received 0,25 $mgkg^{-1}$ of bupivacaine (0,5% Bupivacaine hydrochloride; Aguettant, France) to each nerve;
- Group B (13 subjects) received 0,25 $mgkg^{-1}$ of bupivacaine (0,5% Bupivacaine hydrochloride; Aguettant, France) mixed with 0,25 μgkg^{-1} of dexmedetomidine (Dexdomitor 0,5 mg/ml; Zoetis, France) to each nerve; the dose of dexmedetomidine was taken from a human study of 2016; [55]
- Group C (8 subjects) received 0,5$mgkg^{-1}$ bupivacaine (0,5% Bupivacaine hydrochloride; Aguettant, France) to each nerve.

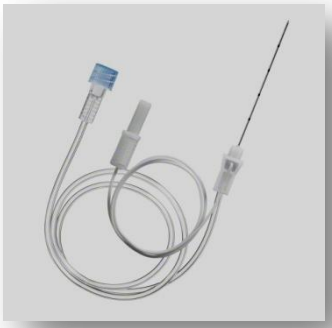
The volume injected to each nerve was 0,1 $mlkg^{-1}$.

- For Group A, the injected solution was prepared by adding the same volume of saline solution to bupicavaine;
- For Group B, the injected solution was prepared in the same way of the previous one, but it was also added dexmedetomidine; the choice of this dose of dexmedetomidine was chose considering a similar human study of 2016 [55];
- For Group C, the injected solution was prepared with only bupivacaine.

The choice of the treatment was made by the same anaesthetist who after has performed perineural block, but he was not involved in the peri- and post-operative

assessments. These latter are been recorded by another anaesthetist unaware of the treatments.

Insulated needles (22 G, 50 or 100 mm Stimuplex-A Insulated Needle; B. Braun, Bethlehem, PA) connected to a peripheral nerve stimulator (Stimuplex HNS12; B. Braun, Germany) were used to perineurally inject the anaesthetic solution.



When the appropriate muscular response was observed at a stimulating current lower than 0.5 mA and higher than 0.2 mA, to avoid intraneural injection, solution was injected at both the femoral and sciatic nerve sites.

Femoral and sciatic nerve blocks were performed as literature described:

- For the sciatic nerve block, the needle was inserted at the one-third the distance between the greater trochanter and ischiatic tuberosity. Flexion of the hock was used to confirm location of the needle close to the nerve. [57]

Figure 13.19 GT-IT line. If the length of this line is divided into thirds, the puncture site is located at a point between the cranial and middle thirds. From: L. Campoy, Peripheral Nerve Blocks in the Dog. Available through Partners in Animal Health, Cornell University, Ithaca, NY, USA. www.partnersah.vet.cornell.edu.

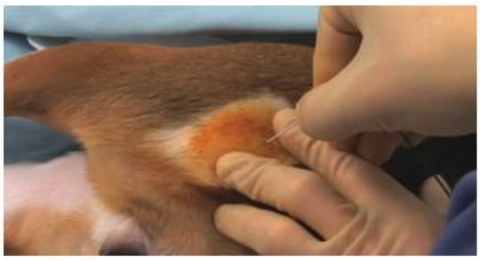


Figure 13.20 Performance of a sciatic nerve block in a dog using the lateral approach. The index and middle fingers of the nondominant hand are used to palpate the greater trochanter and ischiatic tuberosity. The puncture site is located one-third of the distance from the greater trochanter (GT) to the ischiatic tuberosity (IT). From: L. Campoy, Peripheral Nerve Blocks in the Dog. Available through Partners in Animal Health, Cornell University, Ithaca, NY, USA. www.partnersah.vet.cornell.edu.

(Campoy L., Malher S., in **Small Animal Regional Anaesthesia and Analgesia**; Chapter 13: The Pelvic Limb, pagg 199-226. Ed. 2013)

- For the femoral nerve block, the needle is inserted at the intersection of two lines, the first drawn from the spinous process of L6 perpendicular to the spine in dorsoventral direction, the second line drawn from the most cranial aspect of the iliac crest parallel to the spine until it intersects the first line. The needle is directed in a caudomedial direction with an inclination of 30–45° angle through the iliocostalis lumborum muscle and it is advanced until contractions of the quadriceps muscles and consequently extension of the stifle were observed. (58)

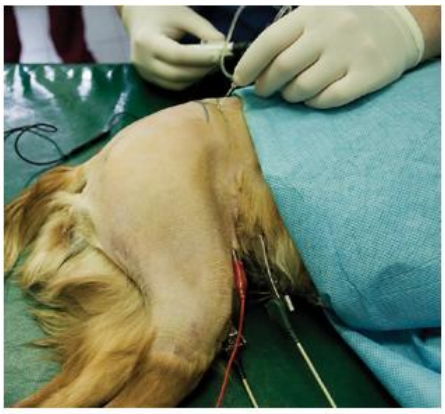


Figure 13.6 Note landmarks on the pre-iliac region. The puncture site is located at the intersection of a line running in a dorsoventral direction at the level of L6 and a second line running parallel to the spine originated at the most cranial point of the iliac crest. Photograph by D.A. Portela.

(Campoy L., Malher S., in **Small Animal Regional Anaesthesia and Analgesia**; Chapter 13: The Pelvic Limb, pagg 199-226. Ed. 2013)

Fentanyl (2µgkg^{-1} IV) was intraoperatively administered as rescue analgesia if HR, RR and MAP values were exceed of 30% the baseline values, despite EtISO 1,4%.
At extubation time if dysphoria was observed:

- Propofol 1 mgkg^{-1} IV was administered;
- Propofol 1 mgkg^{-1} with methadone 0,2 mgkg^{-1} (Comfortan 10mg/ml; Dechra, France) IV were administered if fentanil was intraoperatively injected.

Meloxicam 0,2 mgkg^{-1} (Inflacam 20 mg/ml; Virbac, France) was administered subcutaneously at the end of anaesthesia, if hypotension did not occurred; tramadol 4 mgkg^{-1} (Altadol; Formevet, France) was administered orally 20 hours after extubation and every 8 hours thereafter the observational period, regardless of the pain score.

Monitoring

Data recorded prior to premedication are: age, sex, breed, weight, BCS, surgery procedure, heart rate (HR), respiratory rate (RR), body temperature (T°) and oscillometric non invasive blood pressure (NIBP) with a cuff placed around the antebrachium of the thoracic limb.
Data recorded throughout anaesthesia were: heart rate (HR), respiratory rate (RR), median blood pressure (MAP), carbon dioxide end-tidal ($EtCO_2$), end-tidal isoflurane (EtISO), esophageal temperature (T°) using a multiparameter monitor (Bedside Monitor BSM-5135K, Nihon Kohden Corporation, Japan). Parameters recording began at skin incision and continued every 5 minutes until surgery ended.
The baseline values were recorded when the anaesthesia plane was stable at EtISO 1,1%-1,2%, after nerve blocks and just before surgery started.

Invasive blood pressure was monitored in eighteen patients via a catheter placed in the dorsal pedal artery and the misuration was compared with that non invasive in order to verify the precision of the oscillometric pressure. The measured values were almost superimposable. When systolic and median pressures fell below 80 and 60 mmHg respectively, infusion of Ringer has been increased from 5 to 10 $mlkg^{-1}h^{-1}$, and a bolus of 10 $mlkg^{-1}$ in ten minutes was administered; if this was not enough, a bolus of 2-4 $mlkg^{-1}$ in ten minutes was administered; if all this was not sufficient, cardiovascular support drugs were administered.

Surgery, anaesthesia and extubation times were also collected.

Time to first dose of rescue analgesic, total doses of rescue analgesic required per dog, and GCPS-SF score (Short Form of the Glasgow Composite Pain Scale) at 1, 2, 4, 6, 8, 16 and 20 hours after extubation were recorded.

Dogs received rescue analgesic (methadone 0,2 mg/kg IM) if assigned total GCPS-SF score was ≥ 6 or if at least one category was scored ≥ 3.

To assess the duration of motor and sensory blockades was used a visual clinical evaluation, based on the method described by Portela et al. (2010). Motor and

sensory blockades were assessed at extubation time and then every one hour until total recovery of limb activity.

The proprioceptive response and ability to walk was used to assess **motor blockade** (MB), as follows:

Motor blockade evaluation	
Proprioceptive response	
1. NO EFFECT	Normal motor response
2. PARTIAL LOSS	Delayed motor response and alteration of limb orientation while walking
3. COMPLETE LOSS	Absence of motor response and alteration of limb orientation while walking

(from: Portela DA, Otero PE, Tarragona L, Briganti A, Breghi G, Melanie P. ***Combined paravertebral plexus block and parasacral sciatic block in healthy dogs.*** *Vet Anaesth Analg. 2010 Nov;37(6):531-41)*

Sensory blockade was evaluated by observing the response to a noxious stimulus applied with pressure from a Kelly clamp on the skin over the medial aspect of the thigh (innervated by the sensory branch of the femoral nerve, the saphenous nerve - MT), over the caudal aspect of the metatarsus (innervated by the tibial nerve - CM) and over the third phalanx of the fourth digit (innervated by the common fibular nerve - TP).

Sensory blockade evaluation
Response degree to a painful stimulus
1. NO EFFECT: Normal response to stimulus, with vigorous or rapid withdrawal of the limb and/or vocalization
2. PARTIAL BLOCK: Attenuated response to stimulus, with slower withdrawal of the limb without vocalization
3. COMPLETE BLOCK: Absence of response to stimulus, without limb movement or head movement toward the stimulated area

(from: Portela DA, Otero PE, Tarragona L, Briganti A, Breghi G, Melanie P. ***Combined paravertebral plexus block and parasacral sciatic block in healthy dogs.*** *Vet Anaesth Analg. 2010 Nov;37(6):531-41)*

Statistical analysis

Statistical analysis were performed using SPSS 15.0 (IBM Company, Italy).

Shapiro - Wilk normality test was used to verify the normal distribution of data.

For statistical analysis the first 60 minutes of recorded anaesthesia data during the surgery is only considered.

The data were expressed by median and range.

Changes along the time were evaluated with Wilcoxon Test, while differences between groups were compared using the Kruskal–Wallis and Jonckheere Terpstra tests. Correlation of Pearson was performed between dogs body weight and block duration and between anaesthesia and extubation times. A value of $p < 0.05$ was considered statistically significant.

Results

All the dogs were included in the study and all recovered from anaesthesia uneventfully, without showing any signs of delirium or dysphoria.

Shapiro-Wilk normality test shows that data were not normally distributed.

Significantly differences are found among groups in relation of body weight, with a median value in the Group A higher than the others two groups (p value = 0,002); while no differences are found for body condition scores (BCS) and for age (Tables 1, 2 and 3).

The total anaesthesia and extubation times do not significantly differ among groups. (tables 4 and 5). There are not correlation between both measured times.

There are not statistically differences between the three groups about the amperage of performed femoral block, while there is a mild difference about performed sciatic block, demonstrated by statistically significant for Kruskal Wallis test (p = 0,036), but not for Jonckheere-Terpstra tendency (tables 6 and 7).

Heart and respiratory rates remain (HR, RR) within the normal physiological ranges in all measured time points and in all the three treatments; there are significant differences from baseline and between the three treatments in some time points. (Tables 8 and 9; Graphics 1 and 2).

Median arterial pressure (MAP) is significantly higher than baseline point at almost all time points in Group B; there are significant differences in baseline and time 0 values between the three groups, and in Group B these values are lower than in both other two groups (Table 10; Graphic 3).

It was necessary to increase crystalloids perfusion rate from 5 to 10 $mlkg^{-1}h^{-1}$ in only one subject in Group A, in four subjects in Group B and C. In Group B three of the four subjects also received a 10 $mlkg^{-1}$ crystalloid bolus and one of this a 2 $mlkg^{-1}$ colloid bolus. In Group C three of the four subject also received a 10 $mlkg^{-1}$ crystalloid bolus, one of these received a second crystalloid bolus, and another received a 4$mlkg^{-1}$ colloid bolus; in two subjects 0,1 $mgkg^{-1}$ of ephedrine was administered.

Expired isoflurane concentration (EtISO) in all time points and between three groups is not statistically significant (table 11; Graphic 4). The median scores in all time points and in the three groups were lower than conventional MAC_{BAR}. [59,60]

Statistical analysis of Pain Score shows that there is a significantly difference at 16th hour compared to the 1st hour in Group B, and at 16th and 20th hours compared to the 1st in Group C; no differences are found in Group A. Comparing the three groups there is a significant difference in the 4th hour (Table 12; Graphic 5). About rescue analgesia administration in intra- and post-operatively periods:

- In Group A, one subject received fentanyl two times and another three times in the intra-operatively period, but both do not received analgesics after; one dogs received methadone at 12th hour (GCPS=6);
- In Group B, two dogs received methadone at 12th hour and other two at 16th (GCPS=7, 6, 9, 5; this latter needed analgesia because it received a score of 3 in the section C);
- In Group C two dogs only received intra-operatively fentanyl.

No significant differences are found between the groups with concerning motor and sensory blocks; only in MT3 significant mildly difference is present for Kruskal Wallis test (p = 0,01), but not for Jonckheere-Terpstra tendency (Tables 13-16; Graphics 6-9).

Between motor and sensory block scores and dogs body weights there are some correlations at level:

- TP3, TP2 and TP1 and weights of subjects in Group B (p values = 0,005; 0,006 and 0,006 respectively);
- CM3, CM2 and CM1 and weights of subjects in Group B (p values = 0,004; 0,006 and 0,006 respectively).

Discussion

Trauma and surgery are triggers of a neuro-humoral stress response in all animals, characterized by increased catabolism of carbohydrates, proteins and fats and the release of pro-inflammatory agents.[8]

Studies in humans have shown that perioperative stress response has adverse effects as on immune function, which increases postoperative susceptibility to infections, as well as the predisposition to prolonged ileus and hypercoagulability, with consequently increasing in the risk for ischaemia–reperfusion injury.[54]

One of the major objectives of a veterinary surgeon is to minimize as much as possible the instauration of those changes, by an optimized and patient-personalized analgesic plan. This optimization will improve the pain scores reducing the amount of postoperative rescue systemic analgesia.[39]

In a recent human study of 2014, Di Pede et al., have compared continuous regional block (epidural or extrapleural paravetebral) vs systemic opiates need in a postoperative neonatal intensive care unit. The objective of this study was to estimate the effects of the analgesia techniques over mechanical ventilation, pain score, requirement for additional rescue analgesics, one hour post-surgery heart rate, time-to-pass first stool and to full feed, complications, and duration of hospitalization. They found that loco-regional analgesia was much better than systemic analgesia because associated with a reduced intensity of postoperative care and an earlier full feeding.[61]

In a meta-analysis study, loco-regional analgesia (spinal, epidural, caudal) was compared to general anaesthesia in preterm infants undergoing inguinal herniorrhaphy. The authors found a moderate-quality evidence that spinal anaesthesia may reduce by up to 47% the incidence of postoperative apnoea in infants not receiving additional sedative or analgesic agents. [62] These conclusions are similar to another review, that investigates, on orthopaedic procedures, if regional anaesthesia could reduced incidence of major complications compared to general

anaesthesia. The results were very controversial because some studies demonstrate a positive regional anaesthesia incidence on reducing respiratory and infective complications, where the effect on cardiovascular complications were variable. In the same study, there are some data consistent with a hypothesis that general anaesthesia may be protective against postoperative cognitive dysfunction. A clear and consistent benefit of regional anaesthesia on long-term outcome remains elusive.(63)

In veterinary medicine, loco-regional analgesia, combined with general anaesthesia, is considered a recognized good choice for perioperatively pain management, characterizing by lower intraoperative rescue analgesic doses and a better recovery quality score. (64) this would prevent secondary sensitizations to pain and reduce both requirement for inhalation anaesthetics during surgery and opioid administration after surgery. (65)

Romano et al. (2016) reported in their study that blood glucose and serum cortisol concentrations were similar and unchanged when both peripheral nerve blocks or spinal anaesthesia were performed in dogs undergoing pelvic limb orthopaedic surgery compared to those measured in the control group, while in the group of systemic fentanil was used, their concentration was increased.(54)

Animals undergoing orthopaedic procedures tended to have higher pain scores than soft tissue cases, and it is most severe in the early perioperative period than after 23 hours after extubation, gradually declining as the inflammatory response decreases.(15)

Considering those publications and in order to better focalize the benefit (or not) of loco-regional anaesthesia, in our study we selected only dogs undergoing stifle joint orthopaedic surgery.

The innervation of the stifle is provided by:

- Medial articular nerve, that arises from the saphenous nerve; it occasionally receives supplementary fibers from the obturator and/or femoral nerves. This nerve supplies the medial, posterior, and anterior aspects of the stifle, and may send branches to the anterior attachment of the posterior cruciate ligament.

- Posterior articular nerve, that arises from two separate branches: the directly from the tibial nerve and the second from a muscular branch of the tibial nerve. This nerve supplies the posterior and posteromedial aspects of the stifle joint.
- Lateral articular nerve, that arises from the common peroneal nerve. It serves the lateral collateral ligament and the lateral portion of the stifle joint capsule.(56)

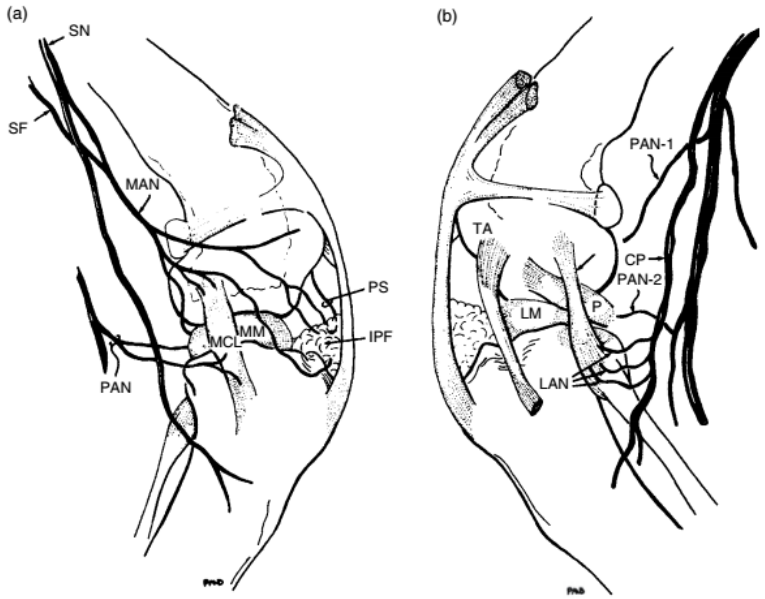


Figure 13.10 (a) Innervation of the stifle, medial view. (b) Innervation of the stifle, lateral view. From O'Connor and Woodbury 1982. Used with permission.

(Campoy L., Malher S., in **Small Animal Regional Anaesthesia and Analgesia**; Chapter 13: The Pelvic Limb, pagg 199-226. Ed. 2013)

In our study we used an electro-location nerve technique to specifies the position of the needle; this technique is preferable rather than using a blind approach in order to inject the minimum volume of local anaesthetic necessary to have a functional block and avoid peri-neural infiltration.(65)

The addition of dexmedetomidine to a local anaesthetic, such as bupivacaine, levobupivacaine and ropivacaine, was found to extend the duration of sensory blockade in peripheral nerves in humans (66,67,55) and in experimental animals (68-70); it

has inhibitory effects on conduction of nerve impulses by blocking the hyperpolarization-activated cation current. [70]

There are some studies in dogs in which dexmedetomidine is used in association with local anaesthetics but they do not evaluate the efficacy and the duration of this association.[71,72]

The results obtained in the only study in dog (Trein and al., 2016), that evaluates the duration of blockade, do not support the hypothesis that perineural dexmedetomidine combined with ropivacaine decreases onset time and increases duration of sensory blockade.[73] The authors concluded that it was possible that the dose of dexmedetomidine used was too low to produce any significant effect, as studies in humans have employed higher doses of dexmedetomidine and the increase in sensory blockade appears to be dose-dependent.[69]

In a study of Lamont & Lemke (2008), onset time to sensory and motor blockade did not differ among treatments, regardless of the route of medetomidine administration; however medetomidine, administered either intramuscularly or perineurally significantly prolonged duration of peak motor block, peak sensory block, and residual sensory block compared with control group. [74]

The dose of dexmedetomidine that we used in our study, more consistent of Trein and al. ones, was chosen considering the human study of Chaudhary et al. 2016, where they found that the block duration in dexmedetomidine group was the double to control group (10.17 ± 2.40 h and 4.16 ± 1.04 h respectively).[55]

In a preliminary study we have associated bupivacaine to dexmedetomidine in ten subjects (data not reported), regardless the kind of surgery procedure, in order to evaluate if the perineural administration of this dose of dexmedetomidine could provoke some important haemodinamic changes own specifics to dexmedetomidine, such as peripheral vasoconstriction and reflex bradycardia. [45] We failed to find any significative differences before and after the local anaesthesia block.

During anaesthesia HR and RR remain always in the physiological range, but in some time points we found significant differences compared to baseline, corresponding to the moments of skin incision and/or suture, or arthrotomy.

About MAP there are not significant differences between the three group, except for baseline and time 0. Half subjects (4 of 8) in Group C needed an increase in crystalloids perfusion rate (from 5 to 10 $mlkg^{-1}h^{-1}$) to compensate a light hypotension; three of these four subjects also received a 10 $mlkg^{-1}$ crystalloid bolus over 10 minutes, one of these received a second crystalloid bolus, and another received a $4mlkg^{-1}$ colloid bolus; in two subjects 0,1 $mgkg^{-1}$ of ephedrine was administered. Four subjects of Group B needed an increasing in rate perfusion from 5 to 10 $mlkg^{-1}h^{-1}$; three of this also received a 10 $mlkg^{-1}$ crystalloid bolus and one of this a 2 $mlkg^{-1}$ colloid bolus; in this group hypotension in two cases was correlated with perioperative hypothermia (~32°C). [75,76] One subject in Group A only needed an increasing in rate perfusion. Significant clinical more severe hypotension has been associated with the 1 $mgkg^{-1}$ of bupivacaine (Group C) compared to the other groups probably due to a mild peri-anesthetic vasodilation, strenghtened by bupivacaine sympathetic block. [77]

End-tidal isoflurane does not show significant differences among the groups and the three treatments allowed to maintain a median value of 1,1-1,2%, lower than conventional MAC_{BAR}. [59-60]

During anesthesia period, two dogs both in Group A and Group C received fentanil 2 μgkg^{-1} (two times and three times for Group A; once only for each in Group C). The administration of fentanyl was in correspondence of skin incision, arthrotomy or suture of the skin. These three surgical moments are performed on the medial aspect of leg, which sensibility is covered by the femoral nerve. In some individual, branches from the other nerves, such as obturator and lateral cutaneous femoral nerves, can potentially provide sensory input on this area. This patient's unique innervations associated to different surgical procedures can result in a partial block effect. [78]

Statistical analysis of Pain Score shows that there is a significantly difference at 16^{th} hour compared to the 1^{st} hour in Group B, and at 16^{th} and 20^{th} hours compared to the

1st in Group C; no differences are found in Group A. Comparing the three groups there is a significant difference in the 4th hour.

In Group A one dogs received methadone at 12th hour (GCPS=6), after 4 hours sensory block end.

In Group B, two dogs received methadone at 12th hour and other two at 16th (GCPS=7, 6, 9, 5; this latter needed analgesia because it received a score of 3 in the section C), after respectively 1, 9, 6 and 7 hours sensory block end.

No one subject in Group C received post-operatively analgesia.

About motor and sensory block duration, there are not significant statistically differences among the groups.

One of the limits of this study is probably the non-homogeneous distribution of subjects in the three groups size that might have affected the ability to evidence statistically significant differences, as demonstrated by significantly difference among the groups relatively to body weights and as showed by significantly Pearson correlation between some sensory scores and weights of Group B; in this latter subjects weight range is wider and the median value is lower than the others groups. In fact, it is the only groups with dogs (5 subjects of 13) weighing below 10 kg. It is possible that the reduction of bupivacaine concentration might be affected the functional block as demonstrated by the very short duration of motor and sensory blockade in this subjects, is accordance with Portela et al. study of 2010, probably because a higher concentration of bupivacaine promotes a higher input of local anesthetic to the inner fibers of the nerve trunk, thus producing a more effective and longer block. [79]

This condition has widely influenced the statistical results, lowering the total duration blockade of the Group B.

Motor and sensory blockade in Group A, where half dose of bupivacaine is used, is strangely not statistically different compared to Group C. This probably is in relation with the higher weights of subjects in Group A than in Group C [median (range) = 35 (22-68) and 29 (15,8-36) respectively]; in Group A many dogs also have a BCS higher than subjects in Group C. In obesity patients, pharmacokinetic (PK) parameters changes occurs, drugs clearance is prolonged, drugs dosage is

overestimated (it is calculated in relation of weight), poor perfusion and oxygenation of adipose tissues is present.[80]

Conclusions

On the basis of the preliminary results of this study, the mixture of bupivacaine and dexmedetomidine used for perineural blockage of the sciatic and femoral nerves (0,25 $mgkg^{-1}$ and 0,25 μgkg^{-1} respectively for each nerve) could significantly increase the blockade duration and improving some benefits on arterial pressure stability. To statistically confirm the tendence found by our results a larger and homogenous sample will be indispensable.

Combination of two drugs has also shown a suitable plane of anaesthesia and analgesia.

Appendix

Table 1

Body Weight (kg)			
A	**B**	**C**	**pvalue**
35 (22-68)°	26 (3-48)°	29 (15,8-36)°	°0,002

Table 2

Body Condition Score (BCS) (score)		
A	**B**	**C**
4 (3-5)	4 (3-5)	4 (3-4)

Table 3

Age (Years)		
A	**B**	**C**
4,25 (1-9)	5 (2-15)	3,25 (1,5-7)

Table 1, 2 and 3: median (range) of Body Weight (kg), Body Condition Score and Age of dogs submitted of sciatic and femoral nerve blocks with bupivacaine 0,25 $mgkg^{-1}$ (Group A), with bupivacaine mixed with dexmedetomidine (Group B) and bupivacaine 0,5 $mgkg^{-1}$.

Significant difference between the three groups for Kruskal-Wallis test, and also for Jonckheere-Terpstra tendency (pvalue = 0,022) was only found in body weight.

Table 4

Anaeshesia time (minuts)		
A	**B**	**C**
188 (153-265)	180 (105-240)	192 (125-245)

Table 5

Extubation time (minuts)		
A	**B**	**C**
13 (5-20)	10 (5-15)	14 (10-22)

Table 4 and 5: median (range) of anaesthesia and extubation times of dogs submitted of sciatic and femoral nerve blocks with bupivacaine 0,25 $mgkg^{-1}$ (Group A), with bupivacaine mixed to dexmedetomidine (Group B) and bupivacaine 0,5 $mgkg^{-1}$. No significant differences were found. Correlation of Pearson did not show any correlation between the two times.

Table 6

mAs femoral (mAs)		
A	**B**	**C**
0,32 (0,28-0,48)	0,32 (0,24-0,40)	0,32 (0,24-0,36)

Table 7

mAs sciatic (mAs)			
A	**B**	**C**	**pvalue**
0,32 (0,28-0,38)°	0,36 (0,32-0,48)°	0,30 (0,28-0,50)°	°0,036

Table 6 and 7: median (range) of femoral and sciatic block amperage. There are not statistically differences between the three groups about the amperage of performed femoral block, while there is a mild difference about performed sciatic block, demonstrated by statistically significant for Kruskal Wallis test (p = 0,036), but not for Jonckheere-Terpstra tendency(pvalue =1).

Table 8

Heart Rate (HR) (beats/minute)				
Time (min)	**A**	**B**	**C**	**pvalue**
B	110 (84-140)	91 (62-112)	95 (73-130)	
0	100 (66-136)*	87 (63-111)	91 (68-119)	*0,008
5	98(68-136)*	86 (65-118)	89 (75-119)	*0,023
10	92 (65-139)°	81 (68-119)°	93 (87-134)°	°0,031
15	104 (75-138)	82 (68-119)	94 (65-143)	
20	99 (75-136)	81 (66-112)	93 (70-148)	
25	102 (77-132)	81 (63-109)	88 (68-146)	
30	105 (64-136)°	81 (64-110)°	108 (71-144)°	°0,026
35	104 (61-135)°	81 (70-108)°	109 (68-151)°	°0,013
40	102 (70-135)°	82 (63-108)°	111 (62-150)°	°0,007
45	96 (80-134)°	82 (71-106)°	108 (70-143)°	°0,008
50	97 (70-135)°	82 (72-105)°	110 (75-115)°	°0,024
55	98 (66-138)°	78 (69-105)*°	91 (76-124)°	*0,05 °0,009
60	114 (70-138)°	76 (70-103)°	115 (76-124)°	°0,007

Table 8: median (range) of HR. Significant statistically differences were found:

- *intra-group;
- °between the three groups: significant for Kruskal-Wallis test, but not for Jonckheere-Terpstra tendency.

Table 9

Respiratory Rate (HR) (breaths/minute)				
Time (min)	**A**	**B**	**C**	**pvalue**
B	14 (6-26)	10 (7-19)	9 (7-29)	
0	15 (4-20)	10 (6-19)	10 (5-29)	
5	17 (8-26)*°	10 (7-25)°	10 (5-31)°	*0,04 °0,002
10	17 (9-23)*°	10 (9-31)°	10 (5-33)*°	*0,04 (A) *0,049 (C) °0,002
15	17 (10-23)°	11 (7-32)°	10 (4-33)°	°0,001
20	17 (10-23)°	11 (7-24)°	10 (5-40)°	°0,001
25	17 (10-22)°	11 (6-24)°	10 (7-42)°	°0,006
30	17 (5-21)°	11 (6-26)°	10 (6-38)°	°0,024
35	18 (5-22)°	12 (7-26)°	13 (7-33)*°	*0,026 °0,031
40	17 (7-20)°	12 (6-26)°	13 (9-38)*°	*0,004 °0,024
45	15 (6-21)	11 (7-26)	8 (5-33)*	*0,001
50	16 (8-23)	13 (6-28)	10 (6-33)	
55	11 (4-22)	14 (3-22)	12 (6-36)	
60	16 (9-23)°	11 (7-28)°	13 (6-33)°	°0,036

Table 9: median (range) of RR. Significant statistically differences were found:

- *intra-group;
- °between the three groups: both for Kruskal-Wallis test and Jonckheere-Terpstra tendency.

Table 10

Median arterial pressure (MAP) (mmHg)				
Time (min)	**A**	**B**	**C**	**pvalue**
B	82 (49-115)°	66 (48-87)°	75 (57-113)°	°0,007
0	81 (62-114)°	67 (47-86)°	70 (57-112)°	°0,005
5	81 (63-115)	77 (46-111)*	75 (52-103)	*0,006
10	76 (71-114)	81 (61-118)*	72 (58-103)	*0,003
15	76 (70-115)	80 (61-116)*	88 (55-100)	*0,005
20	76 (72-115)	79 (50-119)*	72 (58-102)	*0,012
25	81 (72-115)	81 (49-114)*	78 (63-96)	*0,007
30	85 (72-115)	80 (55-118)*	87 (58-97)	*0,008
35	90 (76-114)*	80 (50-102)*	78 (57-100)	*0,032 (A) *0,016 (B)
40	83 (72-116)	79 (48-108)*	78 (57-100)	*0,019
45	85 (73-115)	78 (54-107)*	79 (56-95)	*0,012
50	85 (72-113)	78 (50-107)*	75 (47-114)	*0,005
55	86 (74-113)	82 (50-107)*	81 (60-107)	*0,021
60	92 (64-110)	77 (50-107)*	92 (60-107)	*0,046

Table 10: median (range) of MAP. Significant statistically differences were found:

- *intra-group;
- °between the three groups: significant for both Kruskal-Wallis test and Jonckheere-Terpstra tendency

Table 11

End-tidal isoflurane (EtISO) (%)			
Time (min)	**A**	**B**	**C**
B	1,1 (1-1,4)	1,1 (1-1,2)	1,1(1-1,3)
0	1,2 (1-1,2)	1,1 (0,9-1,3)	1,1(1-1,3)
5	1,1 (1-1,2)	1,1(1-1,3)	1,05 (1-1,3)
10	1,1 (1-1,2)	1,1(1-1,3)	1,15 (1-1,3)
15	1,1 (1-1,3)	1,2 (1-1,4)	1,2 (1-1,3)
20	1,1 (1-1,2)	1,2 (1-1,3)	1,15 (0,9-1,3)
25	1,1 (1-1,3)	1,1 (1-1,3)	1,1 (0,9-1,3)
30	1,1 (1-1,3)	1,1 (1-1,3)	1,15 (1-1,3)
35	1,1 (1-1,2)	1,1 (0,9-1,3)	1,2 (0,9-1,3)
40	1,1 (1-1,3)	1,1 (0,9-1,3)	1,2 (1-1,3)
45	1,1 (1-1,3)	1,1 (0,9-1,3)	1,2 (1-1,3)
50	1,1 (1-1,2)	1,1 (0,9-1,3)	1,2 (1-1,3)
55	1,1 (1-1,2)	1,1 (0,9-1,3)	1,2 (1-1,3)
60	1,15 (1-1,2)	1,1 (0,9-1,3)	1,2 (1,1-1,3)

Table 11: median (range) of EtISO.

Statistical analysis of recorded values did not show any differences in all time points and between the three groups.

Table 12

Pain Score (GCPS-SF)				
Time (hour)	**A**	**B**	**C**	**Pvalue**
1	2 (0-2)	1 (1-4)	1 (1-2)	
2	2 (1-2)	1 (1-3)	1 (1-2)	
4	1 (1-2)°	1 (1-2)°	1 (1-1)°	°0,005
6	1 (1-2)	1 (1-4)	1 (1-2)	
8	1 (1-3)	1 (1-4)	1 (1-3)	
12	1,5 (0-6)	2 (1-7)	1 (1-3)	
16	2 (0-3)	2 (1-9)*	2 (1-3)*	*0,03 (B) *0,001 (C)
20	1 (0-3)	2 (1-3)	2 (2-3)*	*0,001

Table 12: median (range) of Pain Score. Significant statistically differences were found:

- * intra-group;
- ° between the three groups: significant for both Kruskal-Wallis test and Jonckheere-Terpstra tendency (pvalue = 0,002).

Table 13-16: median (range) of motor and sensory blockage. No significant differences are found between the groups with concerning motor and sensory blocks; only in MT3 significant mildly difference is present for Kruskal Wallis test (p = 0,01), but not for Jonckheere-Terpstra tendency(p =0,063).

Between motor and sensory block scores and dogs body weights there are some correlations at level:

- TP3, TP2 and TP1 and weights of subjects in Group B (p values = 0,005; 0,006 and 0,006 respectively);
- CM3, CM2 and CM1 and weights of subjects in Group B (p values = 0,004; 0,006 and 0,006 respectively).

Table 13

Motor block (MB) (minutes)			
Score	**A**	**B**	**C**
3	370 (150-675)	300 (60-710)	350 (120-730)
2	632,5 (180-1035)	480 (120-950)	570 (180-970)
1	692,5 (210-1065)	510 (150-1010)	600 (240-1030)

Table 14

Sensory block (MT) (minutes)			
Score	**A**	**B**	**C**
3	310 (150-735)°	260 (100-885)°	438 (200-850)°
2	577,5 (180-1245)	380 (130-945)	660 (360-1090)
1	622,5 (210-1275)	440 (190-975)	720 (390-1150)

Table 15

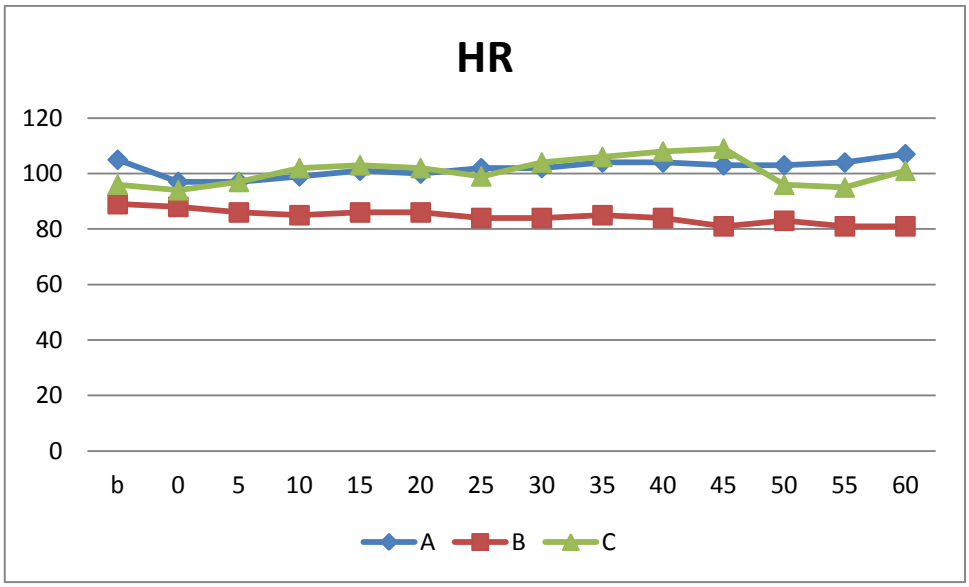
Sensory block (CM) (minutes)			
Score	**A**	**B**	**C**
3	597,5 (150-1095)	330 (90-780)	530 (120-790)
2	752,5 (210-1335)	780 (120- 1190)	660 (240-1090)
1	812 (240-1365)	820 (150-1250)	690 (300-1150)

Table 16

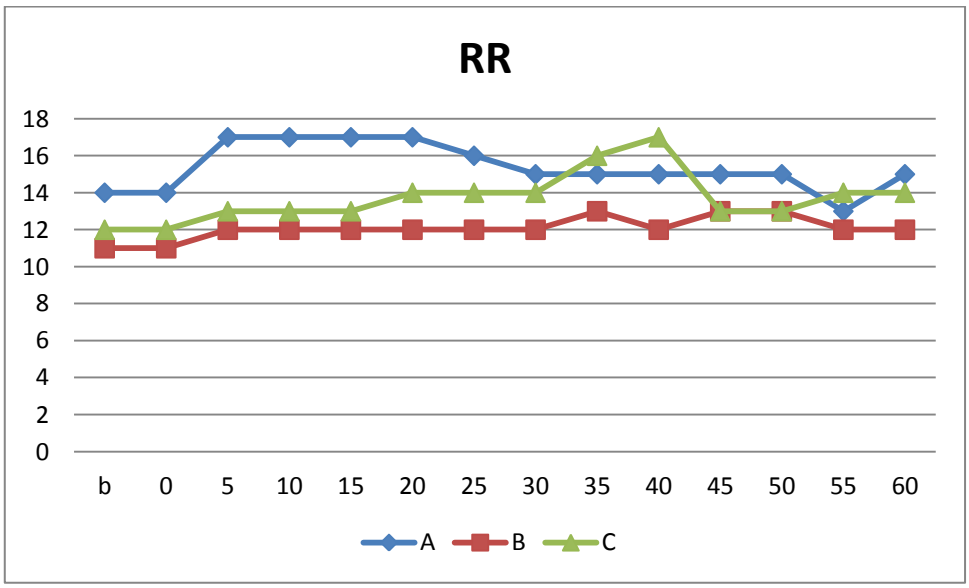
Sensory block (TP) (minutes)			
Score	**A**	**B**	**C**
3	430 (150-795)	300 (90-825)	570 (120-798)
2	722,5 (210-1305)	730 (120-1190)	660 (240-978)
1	782,5 (240-1335)	760 (150-1250)	690 (300-1038)

GRAPHICS

Graphic 1



Graphic 2



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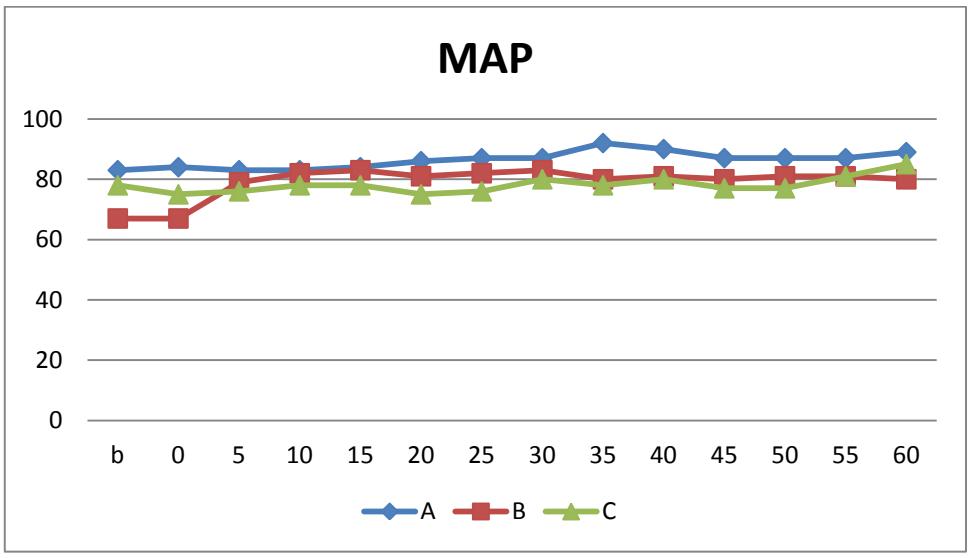

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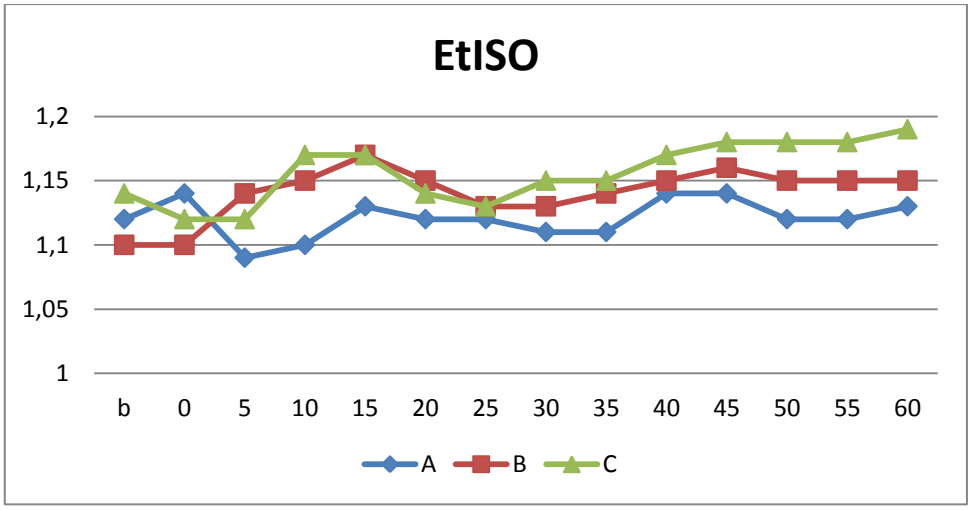
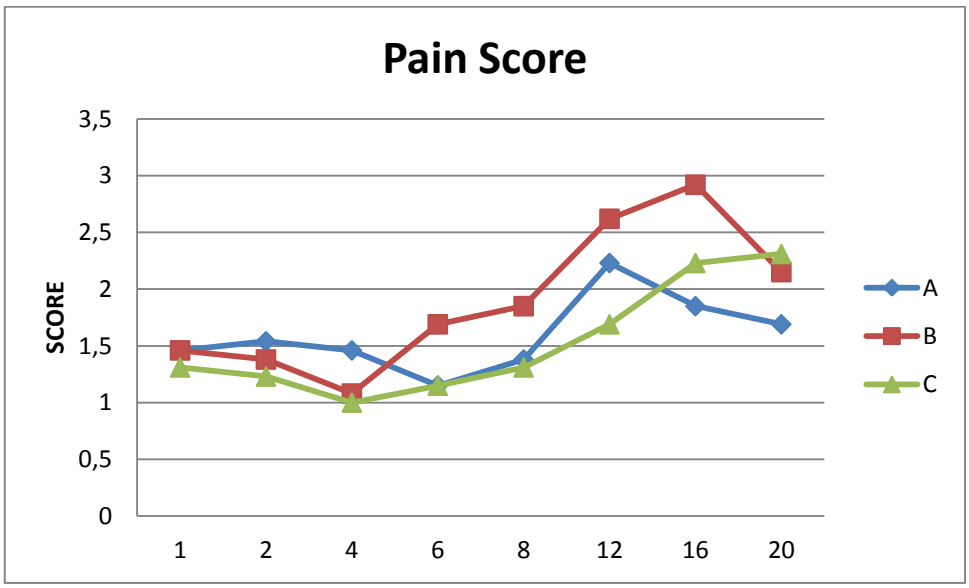


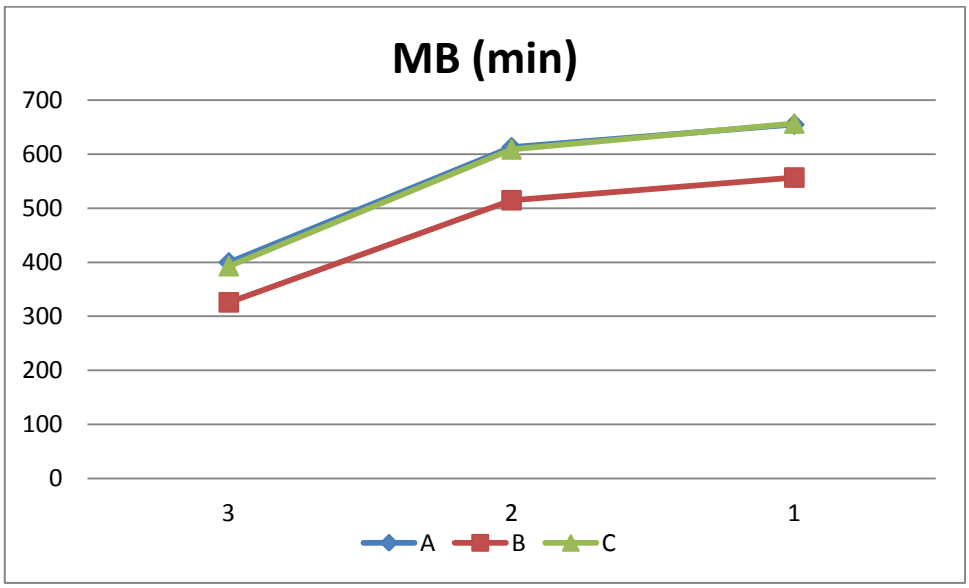
Graphics 1-4: Heart and respiratory rates (HR and RR), and median arterial pressure (MAP) had a linear trend, demonstrating an anaesthesia period stability, in all three groups, with an end-tidal isoflurane concentration between 1,1-1,2 %

Graphic 5

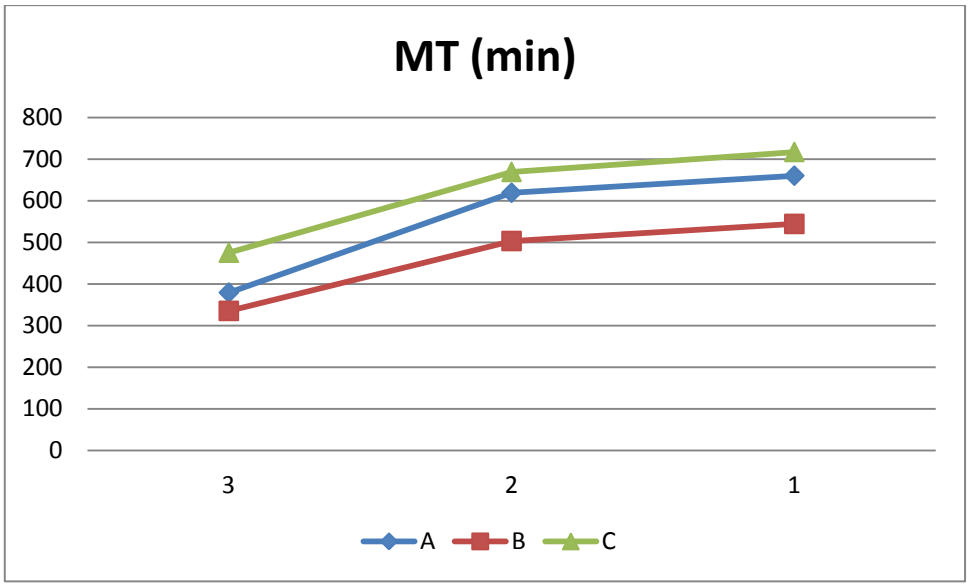


Graphic 5 shows a pain score increasing at 12th and 16th hours after extubation time in all three Groups. In Group C pain scores was lower than the pain scores of the other two Groups; in this group no postoperative rescue analgesia was administered.

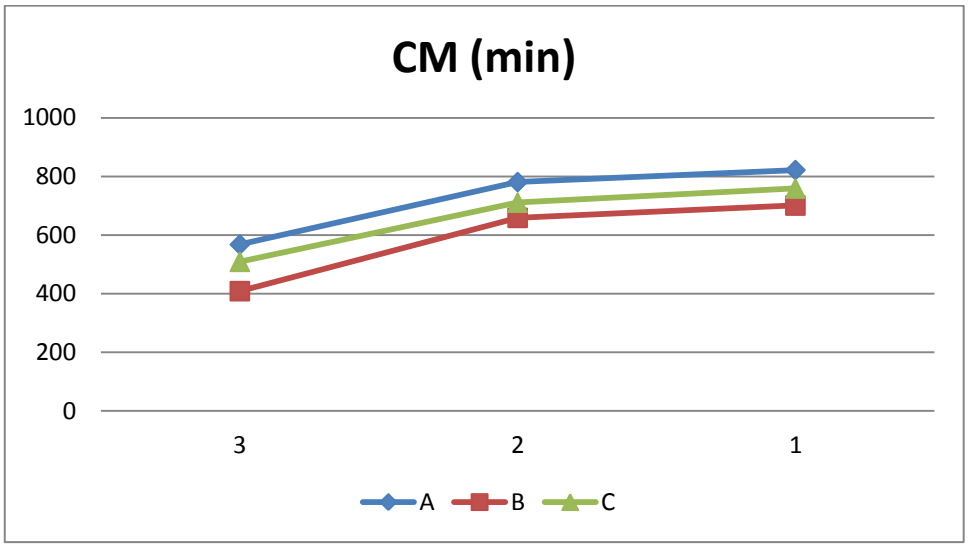
Graphic 6



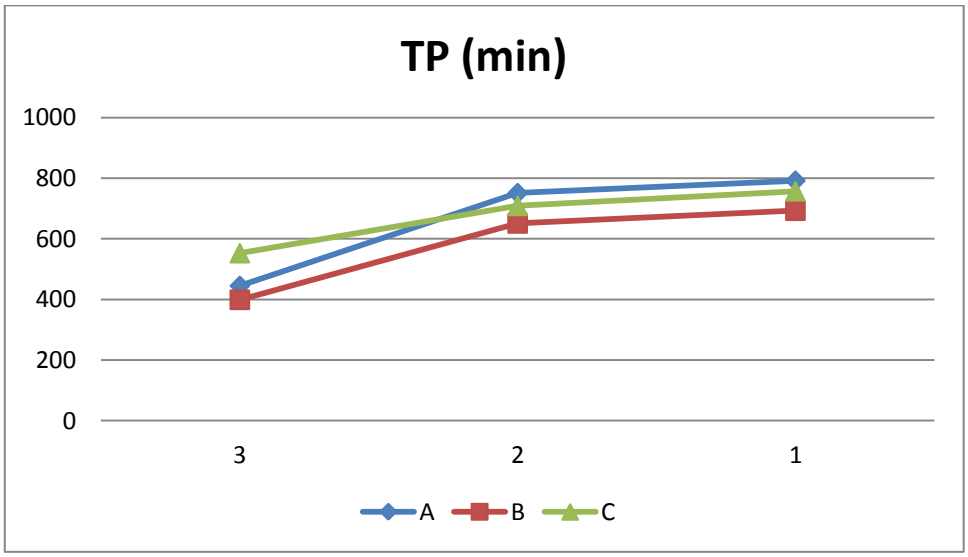
Graphic 7



Graphic 8



Graphic 9



Graphics 6-9: Motor (MB) and sensory blocks (MT, CM, TP) duration (expressed in minutes) were almost superimposable in the three Groups.

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