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A comparative study of different pain management protocols in the perioperative period on cranial cruciate ligament ruptured dogs which undergo TPLO surgery

A perioperatív időszakban használt fájdalomcsillapító protokollok hatásának összehasonlítása TPLO műtéten áteső kutyákon

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Abstract

The successfulness, based on the antinociceptive efficacy, opioid and Isoflurane sparing properties and the consideration of adverse side effects, of a Fentanyl-Ketamine continuous rate infusion (CRI) and certain local anesthesia techniques as add-ons to the ordinary perioperative analgesic drug protocol was examined in the prospective study described in the following. Therefore, 60 dogs which were scheduled for Tibial Plateau Leveling Osteotomy (TPLO), according to a group sequential design, were randomly selected for one of the four study protocols.

All animals were premedicated with Fentanyl, Midazolam and Ketamine. General anesthesia was induced with Propofol and maintained inhalational via Isoflurane delivered in oxygen (O_2). Post-induction, all patients were treated with Morphine intramuscularly.

Additionally, the dogs of the first protocol group were infused with a Fentanyl-Ketamine CRI. To the patients among the second protocol group, no additional add-ons were applied. The individuals which underwent the surgery within protocol group 3 received a local femoral nerve anesthesia via Lidocaine, whereas the dogs within protocol group 4 received an intra-articular stifle joint anesthesia via Lidocaine in combination with a local sciatic nerve and local femoral nerve anesthesia induced with a Lidocaine-Bupivacaine mixture.

Intraoperative Fentanyl boluses were administered routinely 2 – 3 minutes prior to the main surgical actions in the patients of the first two study groups (pre-emptive analgesia), but only after indication in the dogs of the third and fourth study group (rescue analgesia).

The results indicate that there were no significant differences within the first two study groups. Regarding to the dogs of the third study group, especially the antinociceptive efficacy turned out as being the worst. In contrast to those findings, the fourth protocol significantly was characterized by providing successful antinociceptive properties and in general turned out as the best approach.

In conclusion it can be said that the intra-articular stifle joint anesthesia combined with the local anesthesia of the two major nerves innervating the hindlimb are well-functioning add-ons to the ordinary perioperative analgesic drug protocol in dogs during orthopedic hindlimb surgeries which affect the stifle joint.

Absztrakt

Az alábbiakban részletezett prospektív tanulmány célja, az Állatorvostudományi Egyetem Sebészet tanszékére adott időszakban érkező, TPLO műtéten áteső kutya betegeknek az általános protokolltól eltérő anesztézia eljárásainak összehasonlítása. A Fentanil-Ketamin állandó sebességű infúzión túl lokál anesztetikumokat használtunk a mellékhatások mérséklése, az egyéb opioidok és Izoflurán felhasználás mértékének csökkentése, valamint a fájdalomcsillapító hatás fokozása érdekében. Adott időszakban hatvan, TPLO műtétre érkező kutyát választottunk ki, majd a négy vizsgált protokoll csoportjaiba soroltuk őket véletlenszerűen. Minden állatot az általános protokoll részeként használt Fentanil, Midazolam, Ketamin anesztetikumokkal premedikáltuk, majd Propofollal mélyítettük az anesztéziát az intubálhatóságig. Ezt követően az anesztézia mélységét Izoflurán inhalációval tartottuk fent. Az indukció során minden állat intramuszkulárisan Morfiumot kapott.

Az alap anesztéziától eltérően az első csoportban vizsgált kutyák csak Fentanil-Ketamin cseppinfúziót kaptak a fájdalomcsillapító hatás fokozására. A második csoport tagjai semmit sem kaptak az alap anesztézián kívül. A harmadik csoportba tartozók helyileg Lidokaint kaptak a n. femoralis blokkolása érdekében. A negyedik csoport kutyáinál szintén helyi anesztéziát alkalmaztunk: az ízületi üregbe Lidokain került, a n. ischiadicus és a n. femoralis blokkolására pedig Lidokain-Bupivakaint injektáltunk az idegek köré.

Az első két csoport kutyái esetén, a műtét fájdalomcsillapítás szempontjából kritikus pontjai előtt 2 – 3 perccel, rutinszerűen Fentanil bólust adagoltunk (preemptív fájdalomcsillapítás). A harmadik és negyedik csoport állatai esetében csak szükség szerint, a fájdalomérzet megjelenését követően alkalmaztunk ilyen Fentanil adagolást (utólagos fájdalomcsillapítás).

Az eredmények azt mutatják, hogy az első két csoport állatai között nem volt jelentős különbség a fájdalomjelzést illetően, míg a fájdalomcsillapító hatás legkevésbé a csak n. femoralis blokkot kapott kutyák esetében érvényesült. A legteljeskörűbb fájdalomcsillapító hatást szignifikánsan a negyedik csoport alanyai esetében értük el.

Összegzésként elmondható, hogy a helyi izületi érzéstelenítés a hátsó lábat beidegző két fő ideg lokális blokkolásával kiegészítve jó kombináció a szokásos perioperatív fájdalomcsillapító protokolloknak hátsó végtagi ortopédiai műtétek során.

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List of abbreviations

bpm	beats per minute
CaCL	caudal cruciate ligament
CO_2	carbon dioxide
COX	cyclooxygenase
CrCL	cranial cruciate ligament
CrCLD	cranial cruciate ligament disease
CrCLR	cranial cruciate ligament rupture
CRI	continuous rate infusion
DJD	degenerative joint disease
EA	epidural anesthesia
ECM	extracellular matrix
GABA	gamma-aminobutyric acid
HF	heart frequency
IA	intra-articular
IL-1	Interleukin-1
LC	locus ceruleus of the pons
LSEA	lumbosacral epidural anesthesia
MMP	matrix metalloproteases
NMDA	N-Methyl-D-Aspartate
NRM	nucleus raphe magnus of the myelencephalon
NSAIDs	non-steroidal anti-inflammatory drugs
O_2	oxygen
PAG	periaqueductal gray matter of the midbrain
PI	per inhalationem
PN	perineural
PNB	peripheral nerve blocks
RVM	rostroventral medulla axis
SAP	systolic arterial blood pressure
SNP	single nucleotide polymorphism
TP	tibial plateau
TPA	tibial plateau angle
TPLO	Tibial Plateau Leveling Osteotomy
TRAP	tartrate-resistant acid phosphatase

1 INTRODUCTION AND OBJECTIVES

The cranial cruciate ligament rupture (CrCLR) is among the most common canine orthopedic diseases [1]. High-risk breed dogs (Newfoundland, Rottweiler, Labrador Retriever, Bulldog and Boxer) are affected with an incidence of up to 2,610 / 100,000 individuals per year, which emphasizes that this condition is more common in dogs than in humans [2]. For the surgical treatment, the TPLO is a routinely performed technique which procedure stimulates the patients' nociceptive pathway via multiple and different tissue damaging manipulations [3].

The balanced anesthetic and multimodal analgesic protocol which is used ordinarily in the Small Animal Clinic of the University of Veterinary Medicine Budapest is composed of systemic Fentanyl, Midazolam, Ketamine, Propofol and Morphine administration as well as inhalational Isoflurane application. However, this protocol has limitations to successfully control incoming nociceptive stimuli, especially these generated during invasive orthopedic surgeries, such as the TPLO. Prominent disadvantages are huge cardiovascular parametric elevations which represent intraoperative nociception as response to the surgical actions.

The treatment of such a state via the use of commercial systemic analgesic drugs is accompanied by certain dose-related adverse effects which tend to appear at individual variable threshold dosages. Fentanyl is a very potent mu-opioid receptor agonist which can be re-administered, but simultaneously causes cardiovascular depression [4]. Also Ketamine comes along with certain side effects, for instance catalepsy, muscle hypertonus, salivation and cardiovascular stimulation or depression [5, 6].

Consequently, prominent cardiovascular parametric fluctuations and especially Fentanyl-induced bradycardias were frequently detected during the TPLO surgeries. Therefore, the prospective clinical comparative study, consisting of four different analgesic protocols, has been carried out to evaluate the efficacy of a Fentanyl-Ketamine CRI and certain local anesthesia techniques as add-ons to the ordinary perioperative analgesic drug protocol. The objective of the study was the establishment of a successful multimodal antinociceptive management which may enable a beneficial opioid-sparing effect.

2 LITERATURE REVIEW

2.1 Canine stifle joint

2.1.1 Anatomical and functional overview of the canine stifle joint

The complex stifle joint is build-up by the femoropatellar and the femorotibial joint. The first one mentioned acts as a functional sliding joint, which synovial membrane forms one joint recess. In contrast to this, the composed femorotibial joint is a functional spiral joint and forms a lateral as well as a medial joint recess. There is a physiological communication between all three joint recesses. Within the joint cavity, one fibrocartilaginous meniscus is fixed lateral and medial between the femoral and tibial condyles' articulation surfaces. The menisci serve as energy absorbers and they are of great importance for compensation of the normally present stifle joint incongruity.

The physiological stifle joint angle in dogs during standing position is about 105 – 160 ° [7]. During the hindlimb weight bearing phase, femorotibial compression loads arise as a consequence of the interaction of the ground's resistance force and the traction originated by contraction of the femoral quadriceps and gastrocnemius muscles [8]. Since the dogs' proximal tibial plateau (TP) has a physiological caudodistal inclination, the mentioned compression loads are converted into a cranially directed tibial translocation movement in relation to the femur. The thereby created shear force is termed cranial tibial thrust [8, 9]. In healthy dogs, the cranial tibial thrust is counteracted predominantly by the intact cranial cruciate ligament (CrCL). Moreover, active (muscles and tendons) and passive (ligaments, menisci and the joint capsule) structures contribute to maintain the joint stability and limit movements to flexion and extension on the sagittal plane [1]. Rotatory movements during joint extension are counteracted by the two collateral ligaments, while the cruciate ligaments limit rotatory movements during flexed joint position [7]. The described canine stifle joint biomechanism is illustrated in Figure 1.

Individual differences have been found in the degree of the slope of canines' TP. A study of Seo et al. summarized tibial plateau angle (TPA) values varying from 18,1 – 25 ° in healthy dogs. The TPA is measured on a mediolateral projected X-ray by determining the angle arising between a line which represents the TP and a line that is perpendicular to the tibia's long axis on a sagittal plane [10]. Figure 3 shows the radiographic TPA measurement.

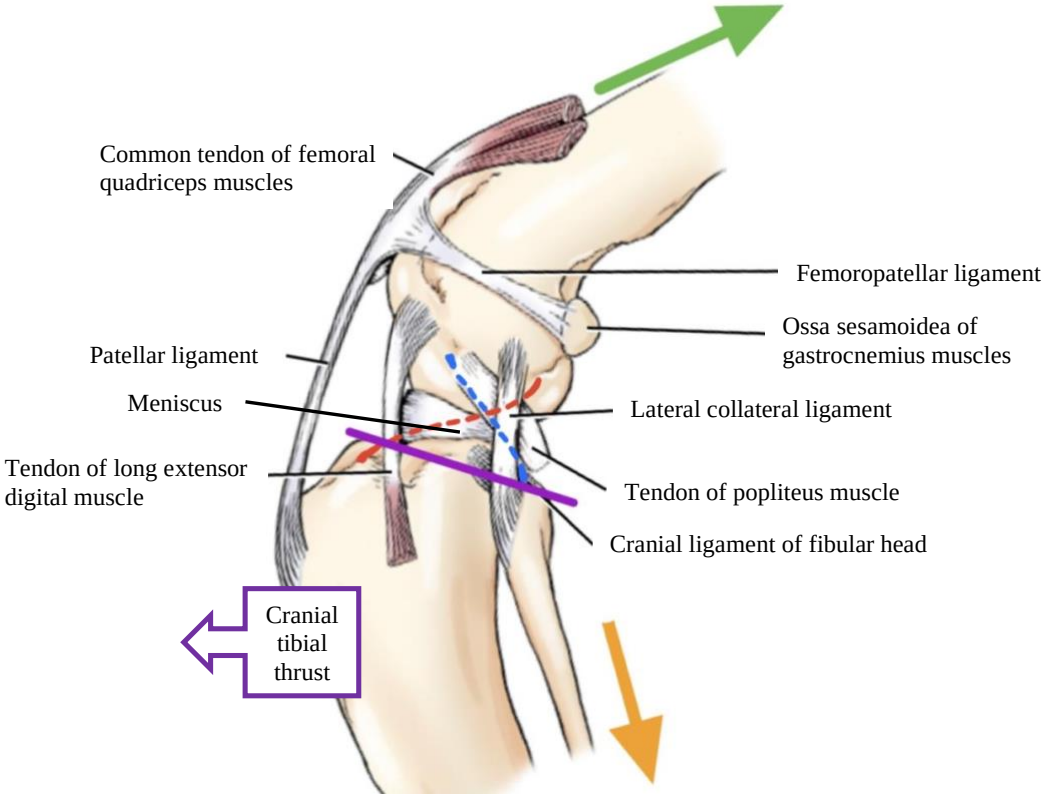


Figure 1: Illustration of the physiological stifle joint biomechanism in canines

Femorotibial compression loads arise during hindlimb weight bearing.
The gastrocnemius muscles cause traction towards the ground (orange arrow), while the femoral quadriceps muscles cause traction towards a dorsocaudal direction (green arrow).
The physiological slope of the TP converts these loads into the cranial tibial thrust.
This cranially directed tibial translocation movement is prevented by the cranial cruciate ligament, menisci and joint capsule as passive restraints as well as the flexor muscles as active restraints.

(Own modified figure of original picture taken from [11 p 72])

2.1.2 Innervation of the stifle joint

Certain nerves of the lumbosacral plexus provide branches to the stifle joint. The mixed (motoric and sensory) femoral nerve (originates from L4 – L6) is accompanied by the femoral vessels. This neurovascular bundle leaves the abdominal cavity via the femoral canal and emits the exclusively sensory saphenous nerve commonly at the proximal level of the femoral bone. The saphenous nerve travels into distal direction on the medial site of the hindlimb.

The mixed sciatic nerve (originates from L6 – S2) passes over the greater ischiatic notch and then continues caudally of the coxofemoral joint and the greater trochanter. On the lateral site of the hindlimb, the nerve runs embedded in muscles into distal direction and bifurcates into the tibial nerve and common peroneal nerve generally at the mid-level of the femoral bone [12].

Particularly, the stifle joint and its periarticular tissues are innervated by three major articular nerves which originate from the saphenous nerve, tibial nerve and common peroneal nerve [13]. Figure 2 provides an overview of the nerve branches.

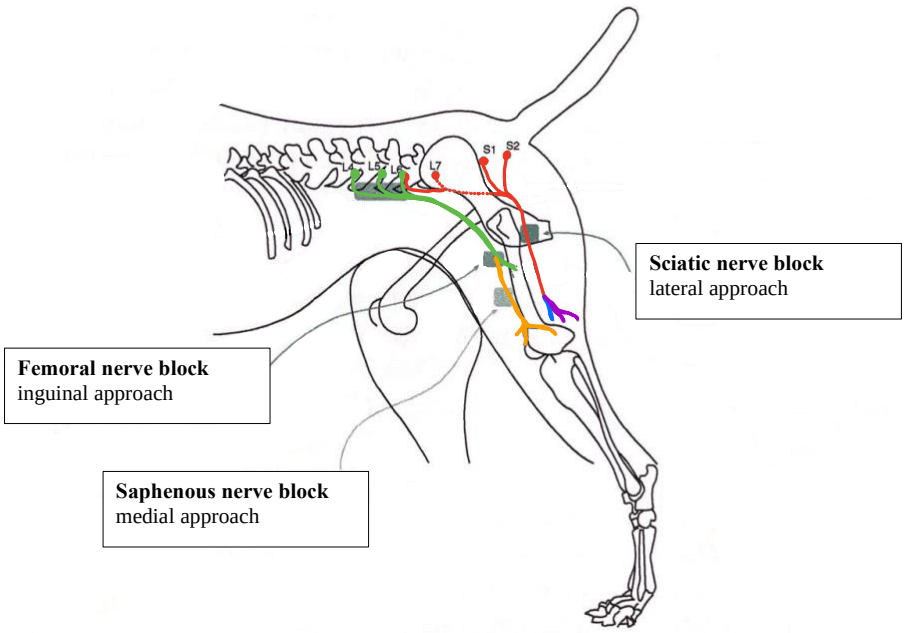


Illustration of the stifle joint innervation and approaches for the related local nerve blocks
Green = femoral nerve
Orange = saphenous nerve
Red = sciatic nerve
Blue = tibial nerve (medial)
Purple = common peroneal nerve (lateral)

Figure 2: Overview of the stifle joint innervation

(Own modified figure of original picture taken from [14 p 229])

Medial articular nerve

The medial articular nerve branches off from the saphenous nerve and serves as the dominant nerve of the stifle joint [13]. In some dogs, it also receives fibers originating from the obturator nerve (originates from L4 – L6) [14]. By the medial articular nerve innervated structures are the medial collateral ligament, the anterior, posterior and medial aspects of the joint capsule, the infrapatellar fat pad, both cruciate ligaments and the meniscal horns [15].

Lateral articular nerve

The common peroneal nerve emits the lateral articular nerve at the level of the fibular head. This nerve mainly innervates the lateral collateral ligament, the superior tibiofibular joint and the lateral aspect of the joint capsule [15].

Posterior articular nerve

The posterior articular nerve originates directly or indirectly, via a muscular branch, from the tibial nerve [13]. Compared to the medial articular nerve, the posterior articular nerve is smaller in size and beside its variations regarding to the point of origin and number of roots, it may even be absent in some individuals [15].

2.1.3 CrCL morphology, anatomy and function

The centrally and intraarticularly localized CrCL originates from the medial surface of the lateral femur condyle, rotates on its own longitudinal axis and then inserts at the tibial central intercondylar area [8]. It is made of ligamentocytes which form multiple collagen bundles that are aligned in a special orientation based on their function [16]. The craniomedial bundle is taut throughout any phase of joint flexion and extension, while the caudolateral bundle becomes flaccid during joint flexion [17]. A thin synovial membrane (epiligament) envelops both cruciate ligaments and leads them to be placed extra-synovially without direct contact to the synovial fluid and the local immune system.

The CrCL's internal blood supply is developed to a lesser extent compared to the internal blood supply of the caudal cruciate ligament (CaCL). Periligamentous blood vessels originate from the synovial envelope and endoligamentous blood vessels originate from the proximal and distal osteochondral insertion points. The CrCL's central aspect, which is also the zone of initial ligament degeneration, is characterized by the worst blood supply [16].

To summarize the functions of the CrCL, it is important to highlight its significance for maintaining the physiological stifle joint biomechanism since it counteracts the cranial tibial thrust, limits tibial inward rotation and prevents stifle joint hyperextension [1].

2.2 CrCL rupture

2.2.1 Pathogenesis

The CrCL failure may be an acute traumatic rupture caused by agility or other physical activities which are accompanied by excessive stifle joint hyperextension or internal rotation [1, 17]. However, this etiopathogenetic hypothesis in canines is considered of minor importance only [1, 16].

In dogs, the injury primarily develops as the result of chronic degenerative changes which damage the CrCL fibers. Thereby, Niebauer and Restucci emphasized that the term "canine cruciate ligament disease" (CrCLD) is the most suitable for its adequate description. Their hypothesis is based on a multifactorial biphasic pathogenesis that initially develops as a subclinical primary osteoarthritis. This pathologic condition affects the entire stifle joint, including in particular the synovial membrane and the CrCL collagen type 1 fibers.

This primary osteoarthritic process is characterized by infiltration and accumulation of certain aseptic inflammatory products, such as synovial mononuclear cells (B- and T-

lymphocytes, plasma cells, tartrate-resistant acid phosphatase (TRAP)-activated macrophages and dendritic cells), inflammatory cytokines and proteolytic matrix metalloproteases (MMP) [16]. Interleukin-1 (IL-1) isoforms are among the most important cytokines which are involved in such osteoarthritic processes. These molecules are believed to play leading roles in complex enzymatic activation cascades. Subsequently, activated metalloproteases are capable of degrading extracellular matrix (ECM) macromolecules, which results in cartilage degradation [18]. Beside the listed molecules, further proteolytic enzymes accumulate, such as cathepsin proteases, collagenases, stromelysins and gelatinases [1]. Especially stromelysins are involved in certain degradative processes which affect the cartilage and several connective tissue types, for instance proteoglycans and type 1 collagen [18]. Therefore, the ambient ECM of the synovial membrane, joint cartilage and CrCL collagen type 1 fibers undergoes a shift from a balanced state into a state of predominant degradation, which is characterized by proteolysis and collagenolysis. A supporting fact for this hypothesis is that cathepsin K proteinase and TRAP proteins have been found in overexpressed amounts in injured canine CrCLs [1].

Additionally, as a consequence of the joint cartilage degradation, cartilage-derived nitric oxide metabolites accumulate which may facilitate ligamentocyte apoptosis. Interestingly, cells of the CrCL tend to have a greater sensitivity to such kind of damage compared to these of the CaCL [16].

The pre-damaged CrCL commonly is described as partial CrCLR, which already leads to minor stifle joint instability and deterioration of the pathologic osteoarthritic state [17]. Subsequently, the weakened ligament fibers in the mid-section of the CrCL are prone to get ruptured totally, even spontaneously during physical load [16, 17]. Regarding to Niebauer and Restrucci's biphasic theory, the CrCLR which follows the primary and silent phase of osteoarthritis, then, due to the abnormal joint instability, progresses the stifle joint into the second phase of osteoarthritis [16].

Nevertheless, the major etiopathogenetic cause for the primary immune-mediated arthropathy is still unclear. One hypothesis may be early damage of the normally shielding synovial membrane, which leads to direct exposure of the degenerated CrCL collagen type l fibrils to the synovial fluid. The collagenous debris may act as antigens and may trigger the local immune system to produce synovia-bound and circulating anti-collagen autoantibodies. A further important factor is that the CrCL's end-arterial microvasculature promotes the deposition of circulating immune complexes [16]. However, a study of de Bruin et al. has shown that not all CrCL diseased dogs with high synovial antibody titers

developed a CrCLR in the contralateral stifle joint. Therefore, it still remains questionable if the activated auto-immune response is considered as an etiological or a secondary event [19].

Diseased dogs commonly develop a time-delayed CrCLR in the contralateral stifle joint as well, since the largely idiopathic pathologic conditions usually affect both stifle joints [17]. Several studies have shown that 40 – 50 % of the patients, sometimes even more, end up with a rupture of the contralateral CrCL within a period of 1 – 2 years [16, 17].

2.2.2 Risk factors

Considered as a multifactorial condition, it seems like there might be a close relationship between the CrCL degeneration and the presence of certain risk factors [17].

In general, the listed main dog breeds suffering from the CrCLD are the Labrador, Newfoundland, Rottweiler, Neapolitan Mastiff, Saint Bernard, Chesapeake Bay Retriever, American Staffordshire Terrier, Akita, Boxer and Bulldog [1]. Regarding to the age, the reported average of the spontaneous CrCLR is 5 – 7 years, with a peak typically at younger age in large and high risk breed dogs [1, 8].

Significant predisposing stifle joint conformations are a steep TPA, a narrow femoral intercondylar notch and a relatively small width of the tibial tuberosity [1, 2, 16]. Another described predisposing anatomical feature is an hyperextended hindlimb, which consequently is accompanied by a greatly opened stifle joint angle. Such anomalies are typical findings in the Chow-Chow, Rottweiler, American Staffordshire Terrier, Boxer and Saint Bernard. In contrast to the mentioned large dog breeds, the CrCLD in smaller sized dogs typically is the consequence of a genu varum abnormality and a patellar luxation, especially grade lV [1].

Furthermore, an underdeveloped femoral quadriceps muscle has promotive impacts to the cranial tibial thrust [1, 2]. Inactivity and poor muscle development in general are unfavorable for the joint stability and the periarticular soft tissue strength, while obesity causes greater stress to the joint and thereby is considered as a facilitating factor for the disease formation [1, 16].

Linked to the gender, bitches tend to be present at a higher incidence rate compared to male dogs, since female sex hormones (e. g. estrogen) result in upregulated MMP-mediated collagen degradation [16]. Neutering generally elevates the risk in both genders [8]. Especially early neutering (under 12 months of age), which may delay the tibial growth plate

closure and thereby may be accompanied by the development of a steep TPA, can be a promoting factor [1, 2, 16]. Furthermore, neutering may result in greater activation of intraligamentous luteinizing hormone receptors, which causes an increase the CrCL's laxity and thereby may predispose ligament tears [1].

Some studies could have proven the presence of a strong breed-related genetic predisposition. Genotyping methods have indicated that certain genes which are encoded on the CrCL's morphological level are affected by a single nucleotide polymorphism (SNP). In particular, they are encoded on the collagen strength, collagen stability, ECM formation as well as the organization and elasticity of ligament fibrils. The SNP affecting such genes is a common finding in dog breeds characterized by high incidence rates [1, 16].

Additionally, genes in the Newfoundland and Labrador, which are responsible for the TP angulation and the width of the tibial tuberosity, are prone to be affected by a SNP [1].

Beside the mentioned facts, pre-existing pathologic conditions may affect the stifle joint as well. For instance, an immune-mediated or septic arthritis may promote the CrCLD formation.

The collagenous ligament fibers also undergo a weakening during the physiological process of aging which is accompanied by the loss of fibroblasts and the remodeling of fibroblasts into chondrocytes [8].

2.2.3 Consequences

The CrCLR finally results in stifle joint instability associated with an abnormal joint motion, which deteriorates the degenerative changes and maintains the second phase of osteoarthritis [16]. This initially non-inflammatory arthropathy in other words is called degenerative joint disease (DJD). Characteristic lesions include the damage and loss of joint cartilage, periarticular osteophyte formations, periarticular soft tissue swelling, joint capsule distension and in some cases also a subchondral bone plate sclerosis [17]. Therefore, the long-term outcome probably will be the stifle joint's decreased range of motion [8].

Furthermore, the joint instability predisposes the development of a secondary meniscal injury. Thus, predominantly the medial femur condyle is prone to get displaced into caudal direction during stifle joint flexion, which may fix the caudal pole of the medial meniscus between the femur and the tibia, leading it to be crushed during extension of the hindlimb. If such a lesion is present, it most commonly represents a circumferential or transverse shaped bucket handle tear and its free portion frequently is folded forward [17].

Diseased dogs may manifest with a wide range of clinical presentations, depending on the etiological background [8]. A peracute onset of a non- to partial-weight bearing lameness in most of the cases represents a traumatic injury, while the condition in chronic cases tends to be characterized by a prolonged weight-bearing lameness or an acute non-weight bearing lameness. Affected dogs commonly have difficulties during rising and sitting and prefer to rest on the contralateral leg [17]. After some weeks, there might be a gradual temporary improvement, as long as no meniscal injury has developed. However, the patients won't be able to return to normal pre-injury function.

In summary it has to be highlighted that the leading cause for the chronic lameness is the development and progression of the DJD [8, 17]. An example of such chronic case is shown in Figure 3.

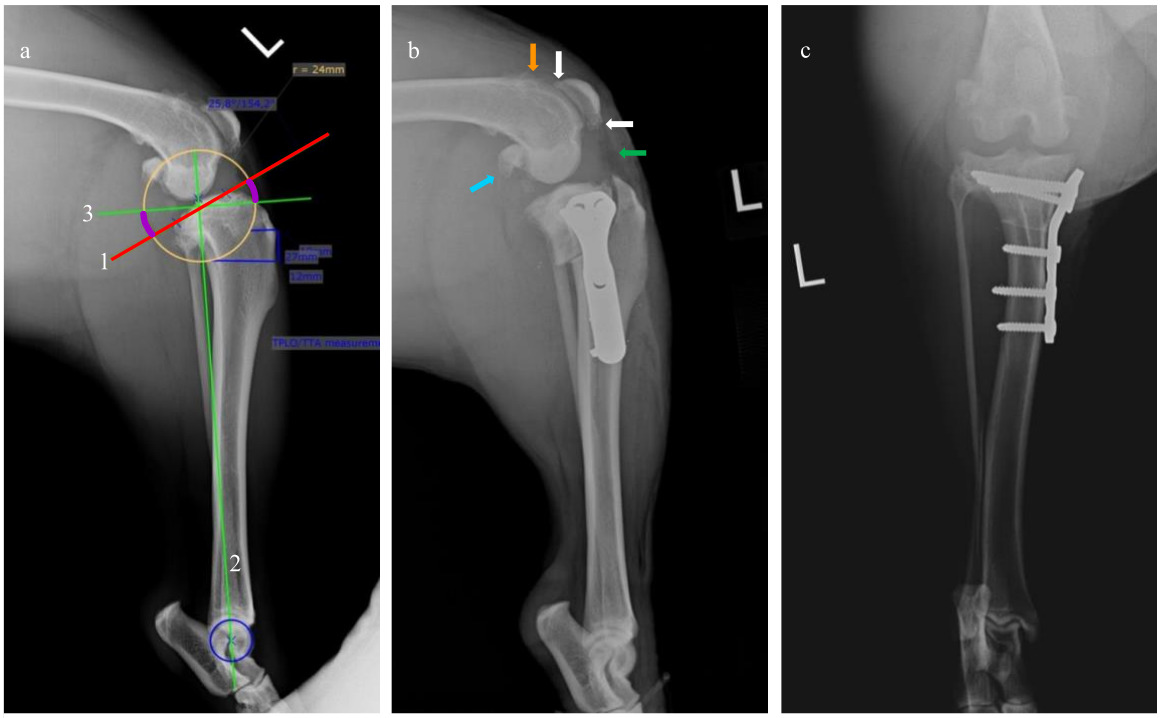
2.3 Features and objectives of the TPLO

Beside the fact that a conservative treatment of the CrCLR in dogs usually won't be successful, the surgical treatment is considered as the gold standard therapeutic approach [16, 17]. However, the development of the secondary phase of osteoarthritis cannot be prevented by any kind of surgery or treatment. Thereby, the primary aim is to re-establish the stifle joint stability and by that to slow down the progression of the DJD, which improves the long-term outcome [16, 17, 20].

A wide range of surgical techniques has been developed. These approaches are classified into intracapsular and extracapsular techniques which achieve the reconstruction of passive joint constraints, and corrective osteotomies which alter the stifle joint's biomechanism [17]. The TPLO, classified among the corrective osteotomies, is suitable for both small and large breed dogs and provides excellent long-term outcomes [21]. The purpose of this surgery is to neutralize the pathological clinical occurrence of the cranial tibial thrust [16, 17, 21]. Since the cranial tibial thrust is directly proportional to the slope of the TP, the objective is to diminish its physiological slope to reach a TPA of approximately 3 – 7 ° postoperatively [17]. This is achieved by performing an osteotomy around the tibial condyle via usage of a semicircular saw blade, followed by rotation of the disconnected proximal tibial bone segment into caudal direction and fixation of the newly created configuration with a special bone plate and screws [22]. Subsequently, the tibial thrust changes from a cranial into a neutral or caudal direction, which then will be counteracted by the CaCL and the active constraints of the stifle joint [17]. The final result of the surgery is presented in Figure 3.

Independently of the used technique, it is recommended to remove the damaged CrCL remnants from the joint cavity, since their metabolites released during the processes of tissue degradation may trigger the osteoarthritis progression [16].

Additionally, meniscal injuries should be treated via a partial or total meniscectomy [20, 22].



Left hindlimb

X-ray a: pre-OP, mediolateral projection
Line 1 = tibial plateau, determined by its cranial and caudal extents
Line 2 = tibial long axis, measured from the center of the intercondylar eminences to the center of the talus
Line 3 = line perpendicular to line 2, passing through the cross-point of line 1 and line 2
Purple = tibial plateau angle (25,8 °), measured between line 1 and line 3

X-ray b: post-OP, mediolateral projection
White arrows = multiple osteophyte formations at the patella
Orange arrow = osteophyte formation at the trochlear ridge
Blue arrow = osteophyte formation at the ossa sesamoidea musculi gastrocnemii
Green arrow = joint effusion compresses the infrapatellar fat pad towards the patellar ligament

X-ray c: post-OP, caudocranial projection

Figure 3 : Pre- and post-OP X-rays taken from a dog participating in the study

This 4 years old female Pitbull Terrier was suffering from a long-lasting history of hindlimb lameness and the chronic pathologic condition has significantly decreased the range of motion of the dog's stifle joint.
The X-rays indicate the typical lesions which represent the manifestation of a severe secondary DJD.

2.4 Nociceptive pathway and pain perception

2.4.1 Definition of pain

The International Association for the Study of Pain (IASP) has set the definition for pain in humans as follows: ‘An unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage’ (1979). Regarding to animals, Molony and Kent published a modification which defines pain in animals as: ‘An aversive sensory and emotional experience representing an awareness by the animal of damage or threat to the integrity of its tissues; it changes the animal’s physiology and behavior to reduce or avoid damage, to reduce the likelihood of recurrence and to promote recovery’ (1997) [23, 24].

2.4.2 Classification of pain

2.4.2.1 Physiological pain

Physiological pain, also called nociceptive acute pain, is the result of current potential noxious stimulation (e. g. pinching the skin) which activates peripheral nociceptors. This state of pain is characterized as normal, transient, localized, adaptive and direct proportional in intensity and duration in relation to the causative stimulus. Physiological pain usually elicits a protective reaction in the individual, which is considered as a beneficial feature [23, 24].

2.4.2.2 Pathological pain

Contrary to the physiological pain, pathological pain is the consequence of severely intense or prolonged noxious stimuli which already have caused significant tissue damage (e. g. osteoarthritis). This state typically tends to be chronic, diffuse, slowly adaptive and non-stimulus specific. Furthermore, it may cause an abnormal hypersensitivity accompanied by extended discomfort as well as rise in morbidity in the affected individual.

Pathological pain manifests as various types, such as inflammatory, neuropathic, nociplastic or sympathopathic pain [23]. Described clinical outcomes may be hyperalgesia, allodynia, expansion of the painful field and protracted pain [25].

2.4.2.3 Types of pathological pain

Pathological pain can be classified based on the injured tissue type and the involvement of the local immune system [24]. However, it commonly occurs as a combined state, referred to as mixed pain. This condition plays an important role in the veterinary field, especially in the case of chronic orthopedic diseases, such as osteoarthritis [24, 26].

Nociceptive pain: Defines pain which is caused by damage of peripheral non-neural tissue, which leads to activation of local nociceptors [23, 25].

Neuropathic pain: Follows a primary injury of the peripheral or central somatosensory nervous system [23].

Nociplastic pain: Describes the presence of idiopathic pain throughout the absence of any clearly detectable tissue injury [23, 24].

Inflammatory pain: Is the consequence of injured, inflamed and/or infected tissue, which is accompanied by the activation of the local immune system [25]. The following chemical environmental changes may lower the nociceptors' activation threshold and also may increase the sensitivity of the affected as well as adjacent non-affected area [24].

2.4.3 Pain components

Perceived pain is a multidimensional experience, which is the result of interaction of sensory, emotional and cognitive components [27, 28].

The sensory component defines that a certain signal will be recognized as being painful [28]. It includes the registration of the site of origin as well as the intensity, duration and quality of the causative stimulus [23]. When tissue damage has been occurring, certain multi-synaptic pathways cause cortical arousal in addition to neuroendocrine and limbic system responses, such as fear, anxiety and behavioral modulation. This is referred to as the emotional pain component [23, 28]. The third pain component is the individual's cognitive response, which describes the higher-level processing of the incoming information [23]. It determines for instance what the patient associates with the perceived signal. This phenomenon is also linked to the conditioned response formation [28].

2.4.4 Neurophysiological nociceptive pathway

All the above described pain components are necessarily involved in the five consecutive steps of the neurophysiological nociceptive pathway, which, exclusively after its completion, results in the conscious perception of pain. This means in particular that the final pain perception manifests due to development and expression of fear, anxiety, emotions and memory in addition to the process of learning, and thereby requires brain analysis and consciousness [23].

If animals are under general anesthesia which prevents a cognitive response, no conscious pain perception can be experienced [29]. However, the first three steps of the nociceptive pathway still can get activated [23]. Therefore, the word pain describes the final sensation in conscious individuals only, while the term nociception is used in anesthetized individuals [29]. A simplified overview of the nociceptive pathway is illustrated in Figure 5.

2.4.4.1 Transduction

The initiating event in the nociceptive pathway is a peripheral noxious stimulus (mechanical, thermal, chemical or electrical) which activates local nociceptors and results in sodium and calcium ion influx into the first-order nociceptive neuron. This process leads to membrane depolarization and conversion of the signal into an action potential [24].

2.4.4.2 Transmission

The generated electric signal travels via afferent axon fibers of the first-order neuron towards the dorsal horn of the spinal cord, where the cell bodies are located.

Thinly myelinated Aδ-fibers conduct fast nociceptive signals with a conduction velocity of 5 – 20 m/sec, which is typical for the transmission of physiological pain. In contrast to that, slow nociceptive signals are conducted via unmyelinated C-fibers with a conduction velocity of 0,5 – 1 m/sec. This happens in case of pathological pain states [23].

The first-order nociceptive afferent axon fibers enter the spinal cord via the dorsolateral fasciculus, predominantly within laminae l – lll of the dorsal horn's gray matter. At this area, the axon terminals form the synapses between the first- and second-order nociceptive neurons [25]. Incoming signals those arriving here trigger the release of certain neurotransmitters into the synaptic cleft. The main responsible excitatory neurotransmitters are glutamate and substance P, which bind to postsynaptic receptors, depolarize and activate the second-order nociceptive projection neurons and thereby transmit the nociceptive signal [24]. The synaptic information transmission is shown in Figure 4.

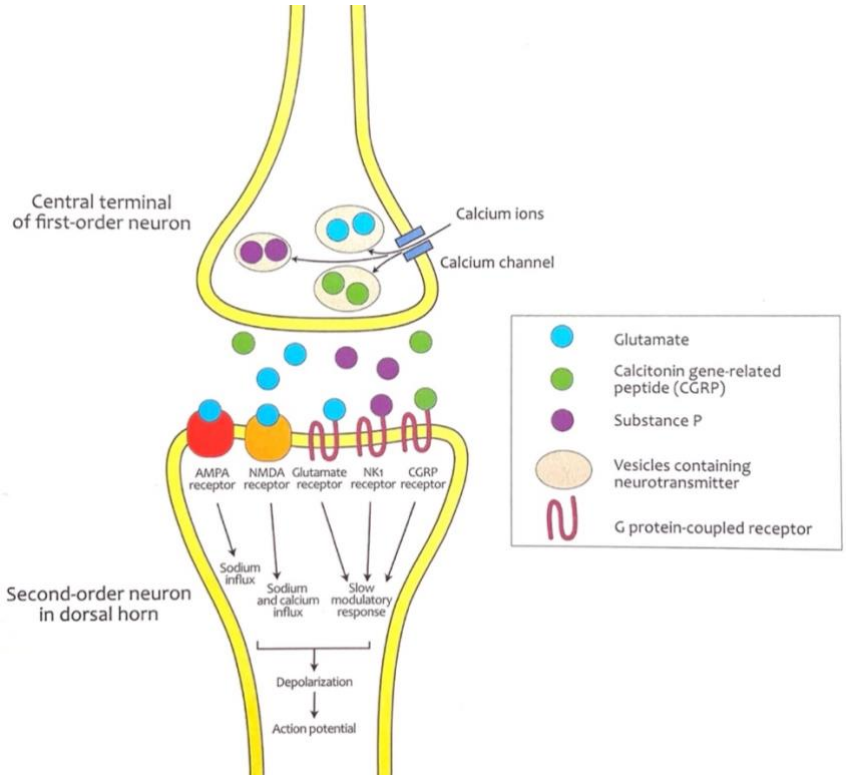


Figure 4: Synaptic information transport between the first- and second-order nociceptive neuron

The arrival of an action potential causes excitatory neurotransmitter release from the first-order neuron into the synaptic cleft. The following neurotransmitter-binding to postsynaptic receptors leads to depolarization of the second-order neuron and thereby transmission of the nociceptive signal.

(Figure taken from [24 p 101])

2.4.4.3 Modulation

Beside the described synapsis formation and information transport to the second-order projection neuron, central modulation processes of the incoming nociceptive signal may happen, which can be both inhibitory or facilitating [23].

This modulation, on the one hand is connected to neurotransmitter-caused effects at the level of the spinal cord, which originate from descending nociceptive pathways that are under control of higher centers in the brain.

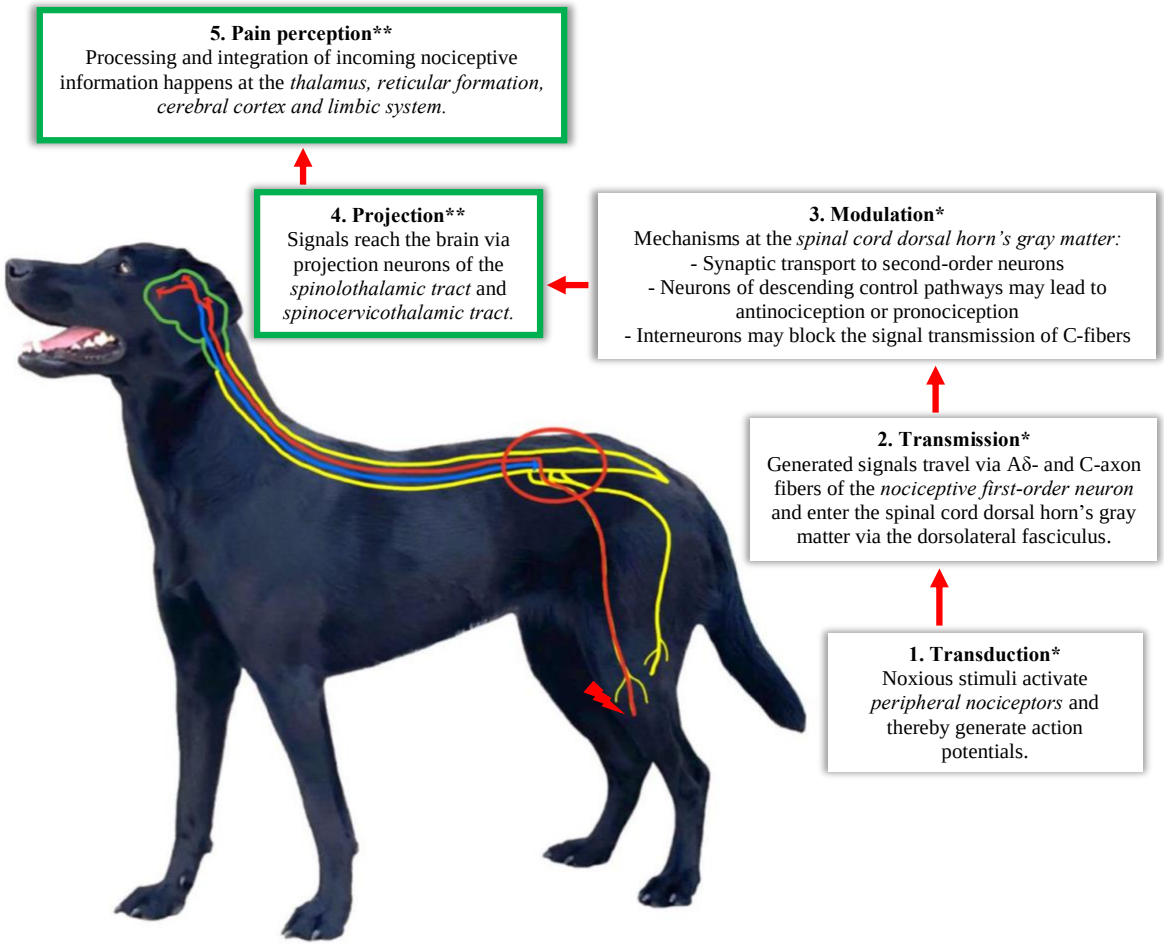
On the other hand, it is caused by the effect of certain interneurons which terminate the signal transmission of C-fibers. This phenomenon is referred to as gate control theory [25].

2.4.4.4 Projection

If the signal, via excitatory neurotransmitter release, is projected to the second-order projection neuron, it reaches the target higher centers via certain ascending pathways [27]. The most important ascending pathways, based on conscious perception and reaction to noxious stimuli, are the spinothalamic and spinocervicothalamic tract. Axons of the spinothalamic tract seem like to be bilateral and multisynaptic, while the axons of the spinocervicothalamic tract most likely run ipsilaterally to the lateral cervical nucleus in the first two cervical spinal cord segments, from where they are projected to the thalamus [25].

2.4.4.5 Perception

The last step involved in the conscious pain perception is based on processing and integration of the incoming nociceptive information at the brain, in particular at the thalamus, reticular formation, cerebral cortex and by means of the limbic system [23, 27]. The key feature is the integration of the animals' cognitive and emotional responses to the initiating noxious stimuli [26].



Red = simplified ascending nociceptive pathway
Blue = simplified descending nociceptive pathway
* = The first steps of the nociceptive pathway may be activated in conscious as well as in anesthetized dogs.
** = The signal projection to the brain followed by the final pain perception requires cognitive, neuroendocrine and limbic system responses and thereby is experienced by conscious dogs only.

Figure 5: Simplified overview of the nociceptive pathway

(Own elaboration, using information from [23–27, 29])

2.4.5 Descending control pathways

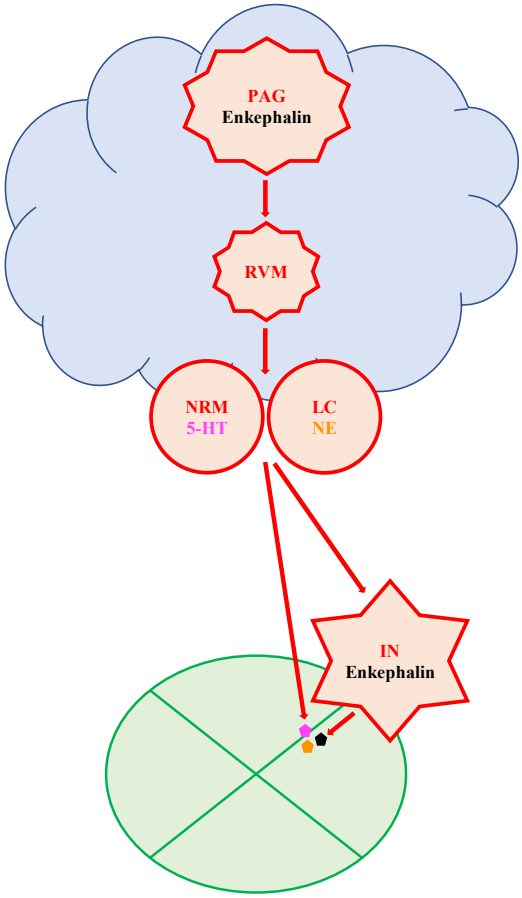
Descending control pathways, based on higher control centers and the action of certain neurotransmitters, are integrated into the nociceptive pathway. Not all of these mechanisms are exactly understood yet. Nevertheless, they participate in either inhibiting or facilitating nociceptive modulation and their investigation is helpful for understanding how analgesic drugs act [23]. Involved structures are several areas of the brain that influence descending neurons which are located at the level of the dorsal column of each spinal cord segment. All participating central areas, neurons and axonal connections thereby form a well-organized network [25].

The periaqueductal gray matter of the midbrain (PAG) receives somatosensory information from higher centers of the brain, such as the cortex, amygdala, thalamus and hypothalamus, as well as directly from ascending nociceptive pathways [23, 30]. Descending pathways originating from the PAG target each spinal cord segment and may inhibit the ascending nociceptive pathway via release of endogenous enkephalin [24].

The PAG furthermore influences other central control areas [25]. Subsequently, the stimulated PAG also excites neurons of the rostroventral medulla axis (RVM), which again are connected to further control centers and can result in either antinociception or pronociception. The RVM, referred to as final transmission point, particularly stimulates the nucleus raphe magnus of the myelencephalon (NRM) and the locus ceruleus of the pons (LC) [23, 25]. These two areas activate descending projections neurons that travel to the spinal cord, where the stimulated NRM elicits the release of serotonin and the stimulated CL causes the release of norepinephrine from descending neurons into the dorsal horn [30]. Norepinephrine binds and activates spinal α2-adrenoceptors, which leads to antinociception, while serotonin may result in antinociception or pronociception, depending on the serotonin receptor subtype [23, 30].

Both mentioned pathways also have the possibility to activate enkephalinergic neurons which are localized at the level of the dorsal horn. Enkephalin released from such interneurons acts on terminals of the first-order afferent nociceptive neurons, where the molecules bind to opiate receptors. This reduces the calcium influx into the cell and subsequently limits the release of the neurotransmitters glutamate and substance P into the synaptic cleft. Opiate receptors additionally are located on the second-order afferent nociceptive neurons, where enkephalin promotes the potassium conductance and thereby causes hyperpolarization of the neuron, which prevents the signal transmission [24]. Figures 6 and 7 provide a simplified graphical summary of the previously described processes.

It can be assumed that the spinal cord's dorsal horn probably has the most important function, since it harbors the mentioned extrasynaptic adrenergic, serotonergic, opioid and gamma-aminobutyric acid type B ($GABA_B$) nociceptive receptors, at which the related endogenous neurotransmitters or exogenous chemical molecules will bind. Thereby, they cause inhibiting or facilitating effects to the incoming nociceptive signal and influence the information transport towards the brain [23, 25].



Simplified model of hypothetic descending nociceptive pathways

Blue = brain
Green = spinal cord
PAG = periaqueductal gray matter of the midbrain
RVM = rostroventral medulla axis
NRM = nucleus raphe magnus of the myelencephalon
5-HT = serotonin
LC = locus ceruleus of the pons
NE = norepinephrine
IN = interneuron

The PAG activates the RVM via release of enkephalin. The RVM furthermore activates the NRM (connected to serotonergic neurons) and the LC (connected to noradrenergic neurons), leading to release of 5-HT and NE into the dorsal horn of the spinal cord.
The descending projection neurons also may activate certain interneurons which cause release of enkephalin.

The molecules released at the synapsis between the first- and second-order afferent nociceptive neurons at the spinal cord's dorsal horn induce effects by binding to their related receptors.

Figure 6: Simplified model of descending nociceptive pathways

(Own elaboration, using information from [23–25, 30])

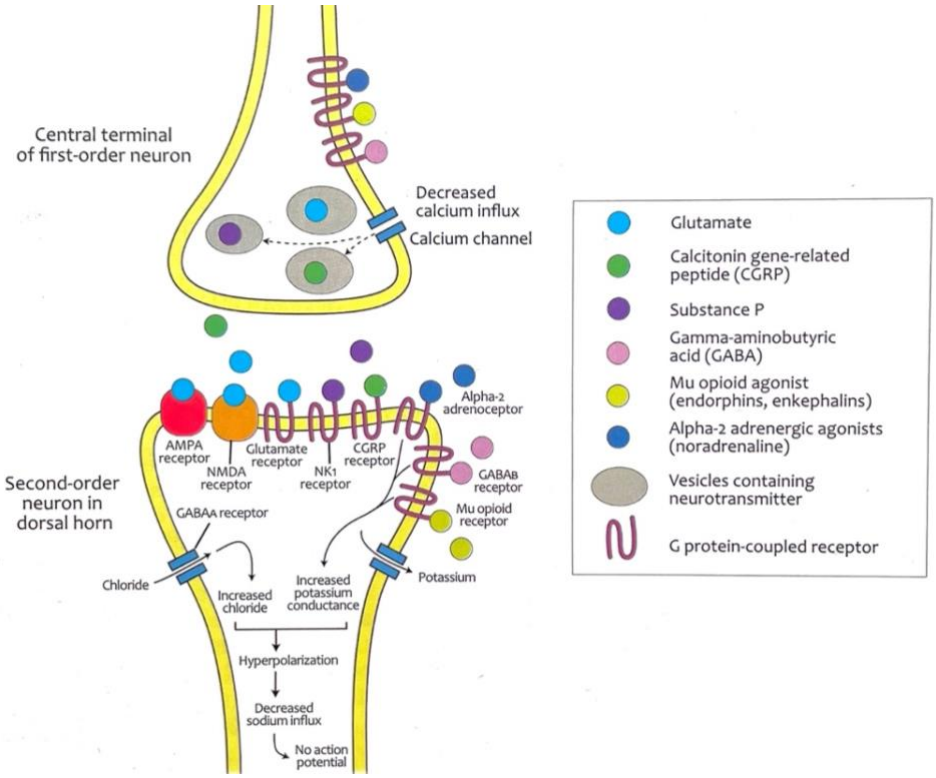


Figure 7: Overview of inhibitory effects between the terminals of first- and second-order nociceptive neurons within the dorsal horn of the spinal cord

α2-adreno, opioid and GABA receptors are located at the first- and second-order nociceptive neurons. After molecule-initiated receptor activation, they cause interruption of the nociceptive signal transport.

(Figure taken from [24 p 102])

2.4.6 Gate control theory

Based on the gate control theory, certain interneurons at the level of the spinal cord, when stimulated, may terminate the continuation of information transport of slower conducting C-fibers which are responsible for the signal transmission of pathological pain. The stimulation of these inhibitory interneurons most probably seems like to be initiated by fast conducting non-nociceptive Aß-fibers [23, 25].

Consequently, since activated interneurons are believed to be enkephalinergic neurons, they inhibit the release of substance P from the C-fibers' axon terminals and thereby close the gate to their related second-order projection neurons [25].

2.4.7 Sensitization of incoming nociceptive signals

The phenomenon called neuronal plasticity describes functional and structural modification processes which affect certain parts of the nervous system as response to previous stimulation or damage [31]. Especially afferent nociceptive C-fibers tend to react with adaptation to such stimulation, which predominantly results in sensitization [23].

In simple words, sensitization processes which affect participants of the nociceptive signal transmission are believed to contribute to the development of the clinical onset of altered pain states. A lowered threshold level, an abnormal increased response to noxious stimuli (hyperalgesia), responsiveness to non-noxious stimuli (allodynia) as well as pain perception in the absence of a stimulus (spontaneous pain) are examples of such states [24].

Primary hyperalgesia is restricted to the site of the current injury, whereas secondary hyperalgesia includes responsiveness to the adjacent non-damaged area [23, 32].

Further described consequences are the formation of a pain memory and the development of chronic pain [32]. Especially osteoarthritic degenerated joints tend to promote the manifestation of peripheral as well as central sensitization processes and thereby facilitate the patient's nociceptive response [33].

2.4.7.1 Peripheral sensitization

Peripheral sensitization affects the nociceptor terminals at the level of the injury [23]. Certain molecules, especially inflammatory mediators and cytokines, such as prostaglandins, bradykinin, neuropeptides and nerve growth factors, referred to as the 'sensitizing soup', are released secondary to local tissue damage [32]. These substances carry out variable actions which, due to amplification of the local inflammation, result in alteration of the local chemical environment [24]. This environmental change causes the peripheral nociceptive afferent neurons to develop an abnormal hyperexcitability and an increased response to incoming stimuli [25].

2.4.7.2 Central sensitization

Chronic or intense nociceptive stimuli, for instance overstimulation originated by secondary osteoarthritis following CrCLD in dogs, tend to result in central sensitization [23]. This phenomenon involves several complex mechanisms, including local environmental neurochemical and cytoarchitectural changes. The outcome observed in such cases may be an exaggerated responsiveness of the nociceptive pathway, which is associated with an increased efficacy in the signal transmission [25].

Such kind of hypersensitive adaptation of affected neurons might be defined as being beneficial, inasmuch it may induce a protective behavior in the individual. On the other hand, it can be characterized as being maladaptive, since any further nociceptive stimulus which incomes after central sensitization has been developing will be perceived as being more painful.

The central sensitization's main key feature seems to be found in activated N-Methyl-D-Aspartate (NMDA) receptors which require both fulfilled voltage-gated and ligand-gated preconditions [23, 32]. Based on this hypothesis, severe tissue injuries (e. g. surgery) or sustained nociceptive input cause prominent glutamate release from presynaptic first-order neurons [32]. Glutamate has a leading role in the pathway of the complex activation cascade of NMDA receptors. In particular, glutamate activates post-synaptic A-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) and kainate receptors. This action causes membrane depolarization and, via phosphorylation of membrane channels as well as activation of certain enzymes (phospholipase A2 and protein kinase C), results in magnesium ion removal from NMDA receptors [24, 32]. Magnesium ions block NMDA receptors during physiological pain states and by this preventing postsynaptic cumulative depolarization, referred to as wind-up phenomenon [32].

The finally opened NMDA receptors cause prolonged calcium ion influx, which facilitates the nociceptive neuronal signal transmission and may lead to prominent enzyme activation as well as altered receptor gene expression, synthesis and activation [23]. Additionally, a pathological activation of microglial cells may occur, which is accompanied by the activation of astrocytes and the release of several inflammatory mediators, such as adenosine 5'-triphosphate (ATP), C-C motif chemokine ligand 2 (CCL2), tumor necrosis factor (TNF), IL-1ß and interleukin-6 (IL-6). These substances also tend to promote the nociceptive neurons' hyperexcitability [25, 26]. Interestingly, the susceptibility for central sensitization mechanisms seems to differ among individuals and these processes also may be influenced by environmental as well as genetic factors [24].

2.4.8 Opioid-induced hyperalgesia

Studies have proven that the administration of full mu-opioid receptor agonists (e. g. Fentanyl and Morphine) in high doses may result in hypersensitivity to incoming nociceptive signals. In such cases, the further administration of opioids may be disadvantageous inasmuch it might result in an hyperalgesic state [23].

The underlying main cause for this hypersensitivity to pain is thought to be found in activated NMDA receptors, which clinically might be detected as a tolerance to given opioids [23, 32]. Therefore, the combined administration of opioids and NMDA receptor antagonists (e. g. Ketamine) is helpful to reduce such a state. This hypothesis consequently underlines the importance of pain management based on a balanced multimodal approach [23].

2.4.9 Intraoperative nociceptive indicators

The mentioned surgical steps being amongst the TPLO (soft tissue destruction, arthrotomy, osteotomy and drilling into the bone) represent several sources of intraoperative nociceptive stimulation to the dog [3]. An inadequate analgesic management, consequently followed by sustained intraoperative nociceptive provocation, is harmful for the patient and thereby it is necessary to recognize signs of acute nociceptive experience immediately [27].

The patient's autonomic responses which are onset at the time of an activated nociceptive pathway are represented by an elevation of the heart and respiratory rate as well as a rise in the peripheral blood pressure [27, 29]. Furthermore, changes in muscular tone and pupillary diameter may be suitable to take into account for determination of the current level of activation of the nociceptive pathway.

If animals perceive acute intraoperative nociceptive input, elevations in hemodynamic parameters of 20 % or more, measured from basal levels, may be detected. However, these parameters are also influenced by further various factors, such as any given anesthetic drugs, fear, stress, a general prominent sympathetic tone or a superficial stage of general anesthesia. Thus, they are not necessarily connected to the reflection of nociceptive perception [27].

2.5 Anesthesia and perioperative pain management

2.5.1 Features of general anesthesia

General anesthesia is defined as the total lack of sensation, which is achieved by a drug-induced, controlled and reversible depression of the central nervous system [34]. Three main characteristics build-up the so called triad of general anesthesia. Unconsciousness defines the lack of perception and memory of any sensory or motor input. Lack of pain sensation, referred to as antinociception, describes the suppressed response to incoming nociceptive stimuli and the third component is specified as total muscle relaxation.

Available anesthetic drugs, especially when used as mono-application and in high doses, are accompanied by a certain degree of cardiovascular and respiratory depression. Therefore, it is indicated to use a balanced anesthesia approach [23, 35]. By definition, this means the administration of multiple different acting agents to be able to decrease the drug dosages and by that to reduce the risk of dose-related complications [34].

The anesthetized animal has to be observed during the entire perioperative period. Principally, the anesthetist is responsible for maintaining the patient's overall homeostasis, ensuring adequate working conditions for the surgeon and in particular providing a successful pain relief management [36].

2.5.2 Drug groups used in the perioperative period

2.5.2.1 Premedication

The major drug groups used for premedication in small animals are tranquillizers (e. g. phenothiazines), sedative-hypnotics (e. g. benzodiazepines or α2-receptor agonists) and opioid analgesics. Their application is beneficial for both the animal and the veterinarian, since they cause sedation and anxiolysis in the animal and therefore facilitate its handling. Further positive effects are the potentiation of analgesic drugs and they also target a smooth post-anesthesia recovery. Based on these facts, the use of premedicative drugs is an essential part of any balanced anesthesia and multimodal analgesia protocol [35, 37, 38].

2.5.2.2 Induction

The final induction introduces the animal into the state of general anesthesia and enables the orotracheal intubation. In canines, injectable anesthetic drugs which cause a dose-dependent depression of the central nervous system are used for that purpose. Such drug groups include substituted phenols (e. g. Propofol), neuroactive steroids (e. g. Alfaxalone), dissociative anesthetics (e. g. Ketamine), barbiturates (e. g. Thiopental) and carboxylated imidazoles (e. g. Etomidate) [5].

2.5.2.3 Maintenance

General anesthesia can be maintained either exclusively by the further provision of injectable anesthetic drugs, via periodic bolus injections or a running CRI, referred to as total intravenous anesthesia (TIVA), or exclusively via inhalational anesthetic agents (e. g. Isoflurane). The combined use of both techniques is named partial intravenous anesthesia (PIVA) [5]. Isoflurane and Sevoflurane are volatile anesthetics which are commonly used in the veterinary field. They cause loss of consciousness but do not act on the nociceptive pathway and consequently do not provide analgesic features. Surprisingly, their exact mechanism of action is not fully clear yet [39].

2.5.2.4 Recovery

The period of recovery after discontinuation of general anesthesia includes the postoperative patient care and especially the further provision of analgesic agents (e. g. non-steroidal inflammatory drugs (NSAIDs)) [35].

2.5.3 Perioperative pain management

An inadequate management of surgical nociceptive provocation on the one hand interferes with the general animal welfare aspects. On the other hand, it elevates the risk for medical complications, negatively influences the recovery and also increases hospital stays [27].
Furthermore, sustained noxious stimuli may lead to sensitization processes, which outcome is more difficult to control. Therefore, the implementation of a pre-emptive analgesia concept may be a beneficial approach for prevention of this pathomechanism. This means that analgesic drugs (e. g. opioids) are administered and consequently provide their effects prior to the onset of nociceptive provocation. For this technique, it is important to keep in mind the duration of action of the given drugs, which may be a limiting factor [23]. A further crucial fact is the adequate timing of the drug application before the start of the surgery [36]. If this pre-emptive analgesia technique is maintained throughout the entire post-operative phase, for as long as the nociceptive stimulus is likely to be present, it is called preventive analgesia [23].

In the praxis, the induction of total lack of nociceptive sensation, termed analgesia in conscious and antinociception in unconscious patients, usually is partially effective only and thereby hypoalgesia is the common true target [23].
The most effective approach to suppress the nociceptive pathway is made on the basis of a multimodal analgesic protocol, which is linked to the concurrent administration of various categories of drugs which inhibit the nociceptive pathway through different mechanisms [4, 29]. This means that interrupting the nociceptive pathway on more than one specific level maximizes the overall pain relief and minimizes the accompanied overall adverse side effects [23].

2.5.4 Analgesic drug groups and their targets in the nociceptive pathway

Figure 8 provides an overview of the most frequently used drug groups and their targets in the nociceptive pathway.

2.5.4.1 Opioid analgesics

Opioids in general are narcotic analgesics which induce dose-dependent effects, in dogs varying from analgesia to euphoria or a sedation-like state.

These agents act on central and peripheral levels, where they bind with different affinity and activity to mu-, delta- and kappa-opioid receptors. The opioid receptors are present in high numbers in the spinal cord's dorsal horn as well as in the PAG and in less quantity in the reticular formation and the limbic system. Kappa-receptors are not being localized at supraspinal levels. Peripheral located opioid receptors might be found in the gastrointestinal tract and in joints, especially in case of local inflammatory processes [23]. Receptors stimulated by opioid agonists inhibit presynaptic calcium channels, which subsequently prevents the release of neurotransmitters that are necessary for the transmission of action potentials (glutamate and substance P). Activated opioid receptors furthermore induce an opening of postsynaptic potassium channels. This results in potassium leakage from the neuron and thereby causes membrane hyperpolarization, which prevents the nociceptive signal transmission [4].

2.5.4.2 NMDA receptor antagonists

Ketamine is a commonly used non-competitive NMDA receptor antagonist. Beside its target as anesthetic agent, it provides analgesic properties when given in sub-anesthetic doses or in form of a CRI. The centrally located NMDA receptors, when antagonized by Ketamine, prevent calcium influx into the nociceptive neuron and thereby interfere with their function in signal transmission [23]. Beside this, the agent also causes some opioid-like actions as well as activation of noradrenergic and serotonergic neurons. As described before, Ketamine, even at sub-anesthetic doses, is a useful choice to reduce central sensitization processes and the risk of developing an opioid tolerance. If given as intravenous infusion, a reduction in the minimum alveolar concentration (MAC) of Isoflurane may be a possible benefit [4].

2.5.4.3 NSAIDs

NSAIDs predominantly act on peripheral levels, where they inhibit cyclooxygenase (COX) iso-enzymes. The blockage of these enzymes prevents the transformation of arachidonic acid, which accumulates as a consequence of local tissue damage, into prostaglandins and thromboxanes. These molecules are among the 'sensitizing soup' and promote peripheral sensitization processes.

Thereby, due to normalization of the nociceptor's terminal surrounding, NSAIDs provide antiphlogistic as well as analgesic properties.

Additionally, since COX products also can be found in the spinal cord, these agents may act on central levels as well [4, 23, 24].

2.5.4.4 α2-adrenoceptor agonists

α2-adrenoceptor sedatives negatively influence the cardiovascular and respiratory system, hence their use as primary analgesic drugs is limited [23]. However, these agents exert analgesic effects predominantly by acting on α2-adrenoceptors located in the dorsal horn of the spinal cord, where they induce hyperpolarization of projection neurons and inhibit neurotransmitter release from primary nociceptive afferent neurons. α2-agonists also tend to cause synergistic interactions with opioid receptor agonists [4, 24].

It is proven that α2-adrenoceptors become expressed during local inflammatory processes in the periphery. Therefore, α2-agonists are believed to act on peripheral levels as well [23].

2.5.4.5 Local anesthetics

Local anesthetics, when injected perineurally, are intended for local nerve blocks. By this method, they bind to neuronal voltage-gated sodium channels and inhibit sodium ion influx. This leads to prevention of membrane depolarization and thereby totally interrupts the peripheral nociceptive signal transport [40]. Furthermore, they may prevent peripheral nociceptor activation [23].

The nerve blockage mechanism is influenced by the nerve fiber's myelination, diameter and firing frequency. The first desensitized fibers are B-fibers, followed by C- and Aδ-fibers and the least ones affected are Aß-fibers. B-fibers are small, myelinated and primarily responsible for autonomic functions. C-fibers are also small, but unmyelinated and they transmit information linked to temperature and low-level dull pain. In contrast to that, group A-fibers are large, myelinated and transmit signals of muscle motor functions, among whose Aδ-fibers conduct fast pain and Aß-fibers are responsible for touch, pressure and nociception [29].

Another possibility to take advantage of the local anesthetic drugs' painkilling effect in dogs is the intravenous administration. Based on this application form, a micro-dose of Lidocaine can be given, which tends to block NMDA receptors at the level of the spinal cord's dorsal horn [24].

2.5.4.6 Gabapentinoids

Gabapentinoids, such as Gabapentin and Pregabalin, are believed to block predominantly N-type voltage-gated calcium channels and additionally they may inhibit presynaptic glutamate release. Since they also tend to modulate NMDA receptors, these agents may participate in prevention of central sensitization processes [23, 24].

Gabapentinoids are the drugs of first choice in case of chronic neuropathic pain states [23].

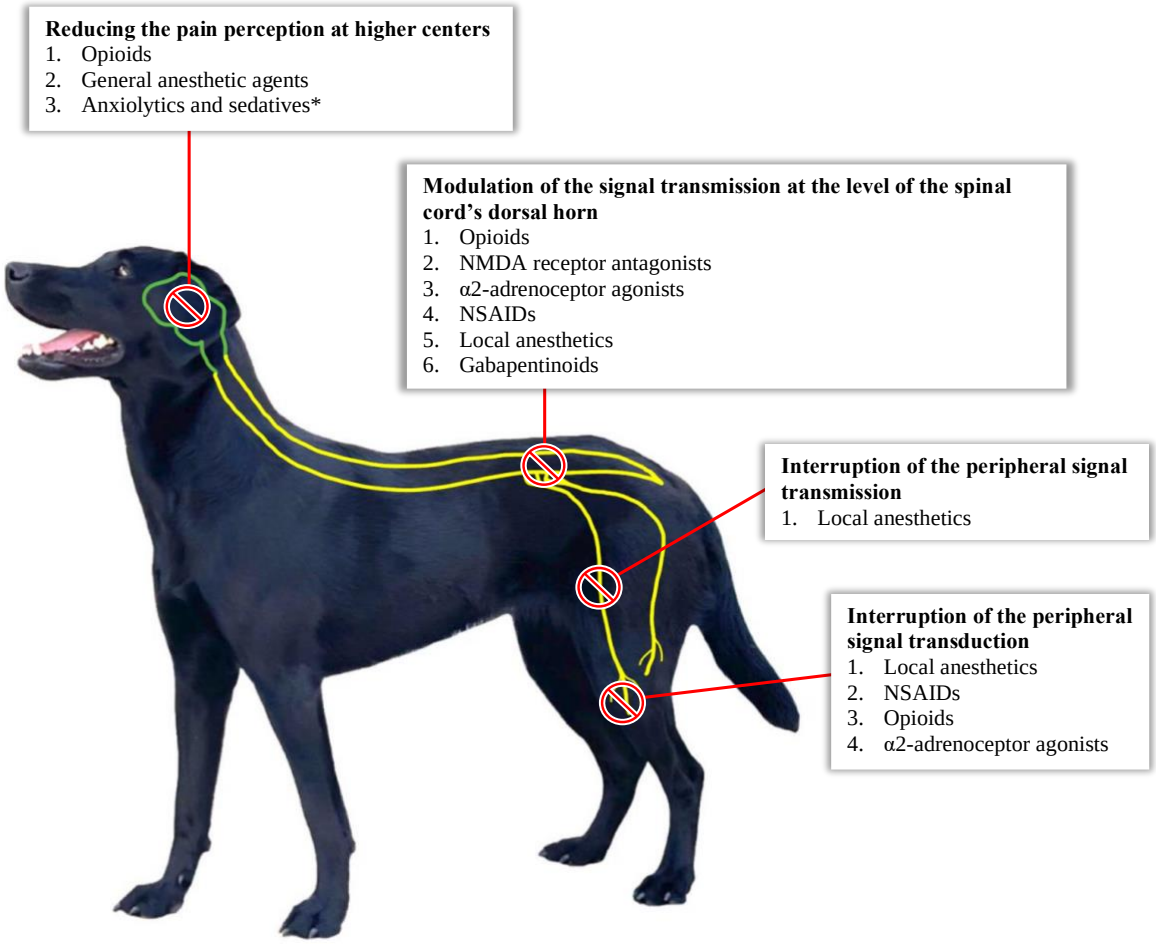


Figure 8: Analgesic drugs and their targets in the nociceptive pathway

(Own elaboration, using information from [23, 24])

3 MATERIALS AND METHODS

3.1 Patients and methods

The prospective clinical comparative study was performed in the Department of Small Animal Surgery belonging to the Small Animal Clinic of the University of Veterinary Medicine Budapest, involving client-owned dogs which were scheduled for TPLO surgery. In total, data from 61 dogs which underwent the TPLO surgery were collected from February 2022 until August 2023. From the mentioned 61 dogs, one patient was excluded from the data analysis, inasmuch as the presence of certain pre-existing conditions necessarily has required minor changes in the protocol. Thus, 60 dogs were fit to participate in the protocols and, via a group sequential design, were randomly selected for one of the four study groups.

3.2 Drugs used in the study protocols

All participating dogs received medication based on the same balanced anesthetic protocol. An overview of the drugs and the related dosages which were used in the study protocols is shown below in Table 1.

Table 1: Overview of the study protocols

	Protocol 1	**Protocol 2**	**Protocol 3**	**Protocol 4**
Premedication	1. Fentanyl 2. Midazolam 3. Ketamine	*5 µg/kg BW IV* *0,25 mg/kg BW IV* *0,5 mg/kg BW IV*		
Induction	Propofol	*2 – 5 mg/kg BW IV, based on effect*		
Maintenance	Isoflurane	*PI, concentration (%) based on effect*		
Post-induction	Morphine Cefazolin	*0,3 mg/kg BW IM* *22 mg/kg BW IV*		
Local anesthesia techniques	Ø	Ø	**1. Femoral nerve block:** Lidocaine *1,5 mg/kg BW PN*	**1. Stifle joint anesthesia:** Lidocaine *0,5 mg/kg BW IA* **2. Sciatic nerve block:** Lidocaine *2 mg/kg BW PN* + Bupivacaine *1,5 mg/kg BW PN* **3. Femoral nerve block:** Lidocaine *2 mg/kg BW PN* + Bupivacaine *1,5 mg/kg BW PN*
CRI intra-OP	Ringer-Lactate	*5 – 10 ml/kg BW/h IV*		
	0,6 mg Fentanyl + 60 mg Ketamine added to 500 ml NaCl *3 ml/kg BW/h IV*	Ø	Ø	Ø
Intra-OP	Fentanyl* *approx. 0,5 µg/kg BW/bolus IV*		Fentanyl** *approx. 0,5 µg/kg BW/bolus IV*	
	Cefazolin	*22 mg/kg BW IV*		
Post-OP	Meloxicam	*0,2 mg/kg BW SC (initial dose)*		

Abbreviations: PI = per inhalationem, PN = perineural, IA = intra-articular
* = pre-emptive analgesia bolus prior to the crucial surgical actions (microarthrotomy and tibial osteotomy) while taking into consideration the patient's response and additional rescue analgesia boluses if necessary
** = rescue analgesia bolus if necessary

3.2.1 Premedication

The first given drug was ***Fentanyl*** *[Fentanyl Kalceks 0,05 mg/ml solution for injection] (5 µg/kg BW IV),* which is a very potent and full mu-opioid receptor agonist. Following intravenous administration, Fentanyl is onset within 1 – 2 minutes and has a short duration of action of 20 – 30 minutes.

This agent is suitable for intraoperative re-administration, which targets the management of acute nociception and therefore is referred to as rescue analgesia bolus (approximately 2 µg/kg BW). Related adverse side effects include vagally mediated bradycardia in addition to minimal myocardial, vascular and respiratory depression [4].

It is important to take into consideration the animal's response to Fentanyl bolus administrations. Based on our experiences in the clinic, intraoperative boluses initially were given with a dosage of approximately 0,5 µg/kg BW/bolus to keep the risk of a Fentanyl-induced bradycardia as low as possible. However, the dosage may be increased, if necessary.

Midazolam *[Dormicum EGIS 5 mg/ml Midazolam solution for injection] (0,25 mg/kg BW IV),* being among the benzodiazepines, was the next intravenously given drug. This agent activates $GABA_A$ receptors and thereby, beside other beneficial effects, causes anxiolysis, sedation and centrally mediated skeletal muscle relaxation [37].

It only causes minor negative influences on the cardiovascular and respiratory system and it is an useful adjunct to Fentanyl and Ketamine. It does not provide any analgesia [38].

The last intravenously applied pre-anesthetic drug was the dissociative agent ***Ketamine*** *[CALYPSOL 50 mg/ml Ketamine solution for injection] (0,5 mg/kg BW IV),* which is onset within 30 – 90 seconds and has an elimination half-life of approximately 60 minutes [6].

Ketamine is associated with several dose-related pharmacodynamic actions. As the name says, it introduces the animal into a dissociative state. This is characterized by profound analgesia, amnesia, catalepsy, muscle hypertonus, hypersensitivity to noises and maintained cranial nerve reflexes (palpebral, ocular and swallowing reflex) as well as active pedal reflexes, occasionally accompanied by transient convulsive-like activity. Additionally, salivation may occur, which may predispose airway obstructions.

Regarding to the cardiovascular system, this agent causes direct negative inotropic myocardial effects as well as direct vasodilation but simultaneously stimulates the sympathetic nervous system. Thereby, the overall expected response in healthy patients

usually will be a mild increase in cardiac output, heart rate and arterial blood pressure. However, in compromised animals, e. g. being in a condition of shock (sympathetic exhaustion) or suffering from cardiac diseases, cardiovascular depression has to be expected to predominate. Beside this, Ketamine tends to induce a transient post-induction apnoea, which may be followed by irregular breathing pattern. This agent furthermore increases the cerebral blood flow as well as the intracranial pressure [5, 6].

3.2.2 Induction

General anesthesia was induced via intravenous administration of ***Propofol*** *[Propofol 1 % or 2 % MCT/LCT Fresenius emulsion for injection or infusion] (2 – 5 mg/kg BW IV)*. To reduce the risk of post-induction apnoea, this drug was injected quite slowly. The volume was given based on effect, to be able to perform orotracheal intubation.

Propofol is rapid onset, already after 60 seconds, but has a short duration of action of approximately 10 minutes. This primarily hypnotic agent acts as agonist on $GABA_A$ receptors and by that facilitates the inhibitory actions of GABA [6]. It provides no analgesic effects [5].

A common adverse effect associated with Propofol, especially when given rapidly, is a transient mild to moderate respiratory depression. This state may last for several minutes and thereby might cause arterial blood oxygen desaturation accompanied by cyanotic mucous membranes. Furthermore, a mild myocardial depression and venodilation, resulting in moderate hypotension, may develop. Propofol tends to decrease the cerebral metabolic rate, perfusion pressure as well as the intracranial pressure [5, 6].

3.2.3 Maintenance

Anesthesia was maintained via ***Isoflurane*** *[Isoflutek 1000 mg/g Isoflurane liquid for inhalational vapor A. U. V.] (PI)* delivered in O_2 via the breathing circuit of the anesthesia machine. The initial concentration, until reaching an adequate depth of general anesthesia, was set between 1,8 – 3 %. Thereafter, the concentration usually could been decreased to lower levels.

Isoflurane may induce some dose-dependent adverse side effects, such as a reduced cardiac output, a drop in blood pressure and respiratory depression. Beside these, it causes irritation

on the respiratory mucous membranes. This agent may be a trigger for the development of malignant hyperthermia. No analgesia is provided by the use of Isoflurane [41].

3.2.4 Post-induction period

All patients received ***Morphine*** *[Morphine Kalceks 10 mg/ml solution for injection] (0,3 mg/kg BW IM)* as intramuscular injection. Morphine is a potent and full agonist with high affinity to mu-opioid receptors and moderate affinity to kappa- and delta-opioid receptors. Its duration of effective analgesia in dogs lasts approximately 2 – 6 hours [4].

Antibiotic support was provided via intravenous application of ***Cefazolin*** *[Cefazolin Sandoz 1 g powder for injection or infusion solution] (22 mg/kg BW IV),* which was re-administered after 1,5 hours.

3.2.4.1 Study protocol 3

The dogs participating in group 3 additionally were treated with ***Lidocaine*** *[Lidocain EGIS 10 mg/ml Lidocaine hydrochloride solution for injection] (1,5 mg/kg BW PN)* as part of the multimodal analgesic protocol. This agent was injected perineurally for induction of a local femoral nerve anesthesia. By this technique, Lidocaine is onset within 1 – 2 (< 5) minutes and has a duration of action of about 1 – 1,5 hours.

The concurrent use of systemic analgesic drugs and local nerve blocks is considered as one of the most effective approaches to achieve a successful blockage of incoming nociceptive signals. Furthermore, this technique enables to lower the risk of dose-related adverse side effects which may be onset in correlation with systemic bolus applications (e. g. opioids) [29].

Potential side effects linked to perineural injections are infections, tissue injuries due to local vasoconstriction followed by tissue ischemia, nerve injuries and hematoma formation. If Lidocaine in anesthetized dogs inadvertently is injected into the intravascular space, beside allergic reactions, systemic concentration-related adverse effects have to be expected, such as respiratory arrest and depression of the cardiovascular system [40].

3.2.4.2 Study protocol 4

The dogs undergoing the surgery within group 4 received an intra-articular stifle joint anesthesia induced with ***Lidocaine*** *[Lidocain EGIS 20 mg/ml Lidocaine hydrochloride solution for injection] (0,5 mg/kg BW IA).* It is known that all local anesthetic drugs cause cartilaginous mitochondrial dysfunction, apoptosis and necrosis. This kind of joint cartilage damage occurs especially in case of pre-damaged osteoarthritic joints. However, the development and outcome are influenced by the chosen active agent, its concentration as well as the exposure time. Compared to Bupivacaine, Lidocaine is the less chondrotoxic agent [40]. Beside this fact, Lidocaine also was preferred because of its shorter duration of action.

Furthermore, all patients in this group received a local sciatic nerve block in addition to a local femoral nerve block induced with a mixture of ***Lidocaine*** *[Lidocain EGIS 20 mg/ml Lidocaine hydrochloride solution for injection] (2 mg/kg BW/nerve block PN)* and ***Bupivacaine*** *[Marcain AstraZeneca 5 mg/ml Bupivacaine hydrochloride solution for injection] (1,5 mg/kg BW/nerve block PN).* Bupivacaine in large nerves is fully onset within maximal 20 minutes and has a duration of action of 4 – 6 hours [29].

The combination of these two agents is beneficial since the intended effect can be achieved faster and its total duration will be prolonged. However, the effect induced by a combination of these two drugs will be shorter when compared to the mono-use of Bupivacaine [42].

Adverse side effects which have to be expected with the perineural application of Bupivacaine are similar to those mentioned in relation to Lidocaine. Important to highlight is that cardiotoxic effects caused by Bupivacaine are present to a greater extent. Compared with Lidocaine, this means in particular a 4 times higher potency to cause myocardial depression and a 16 times higher potency to be arrhythmogenic [40].

3.2.5 Intraoperative period

All animals received ***Ringer-Lactate*** *[Ringer-Laktát Fresenius solution for infusion 500 ml] (5 – 10 ml/kg BW/h IV)* throughout the entire intraoperative period in order to provide hemodynamic support and compensate surgery-related fluid losses.

The dogs of group 1 additionally were infused with the ***Fentanyl-Ketamine CRI*** *[0,6 mg Fentanyl Kalceks 0,05 mg/ml solution for injection* and *60 mg CALYPSOL 50 mg/ml Ketamine solution for injection* added to *Nátrium-klorid 0,9 % Fresenius solution for infusion 500 ml]* at a rate of *3 ml/kg BW/h IV.*

All dogs of group 1 and group 2 routinely received *Fentanyl pre-emptive analgesia boluses [Fentanyl Kalceks 0,05 mg/ml solution for injection] (approximately 0,5 µg/kg BW IV)* intravenously prior to the main critical surgical manipulations (2 – 3 minutes before the microarthrotomy and tibial osteotomy).
According to the patient's response and the surgical actions, the boluses were adjusted individually. Practically this means, if a patient has responded to a given bolus with developing a bradycardic state, further Fentanyl boluses were withdrawn or at least lower dosages were chosen. If required, **Atropine** *[Atropinum sulfuricum-EGIS 1 mg/ml Atropine-sulfate solution for injection] (0,01 mg/kg BW IV)* was given to treat bradycardia.
On the other hand, additional Fentanyl boluses (e. g. during suturing of the joint capsule or soft tissue preparation for the tibial osteotomy) or higher dosages were applied, if necessary.

The dogs participating in group 3 and group 4 received *Fentanyl rescue analgesia boluses [Fentanyl Kalceks 0,05 mg/ml solution for injection] (approximately 0,5 µg/kg BW IV)* intravenously. Consequently, Fentanyl boluses were given exclusively after indication (rise in heart frequency (HF) or systolic arterial blood pressure (SAP) by approximately ≥ 15 % from the previously recorded value (in the following referred to as baseline value) or switching into panting-like respiratory pattern) and not routinely prior to the surgical manipulations By this technique, it was possible to check properly if the local anesthesia techniques have been successful.

3.2.6 Postoperative period

A subcutaneous injection of ***Meloxicam*** *[MELOVEM Dopharma 5 mg/ml Meloxicam solution for injection A. U. V.] (0,2 mg/kg BW SC)* was given to all patients after regaining consciousness, extubation and normalization of the internal body temperature. Meloxicam is a preferential selective COX-2 inhibitor, which provides effective postoperative analgesia for a duration of action of about 24 hours.

The most frequently occurring adverse effects are vomiting, diarrhea, inappetence and gastrointestinal tract ulceration, which predominantly have to be expected in case of long-term applications or high doses. Kidney damage can be induced or aggravated if the patient has been suffering from pre-existing kidney disease or due to impaired renal perfusion.

Further described side effects are hepatotoxicity, teratogenicity and inhibition of platelet activation. The last one mentioned is also caused by COX-2 selective agents, however without a significant clinical outcome. Today's studies linked to NSAIDs-induced chondrotoxicity are controversial but it can be said that currently licensed active agents won't cause significant cartilage damage. Moreover, they are regarded as good choices for palliative osteoarthritis treatment [4].

3.3 Actions carried out in the perioperative period

Figure 9 provides an overview of the actions carried out in the perioperative period.

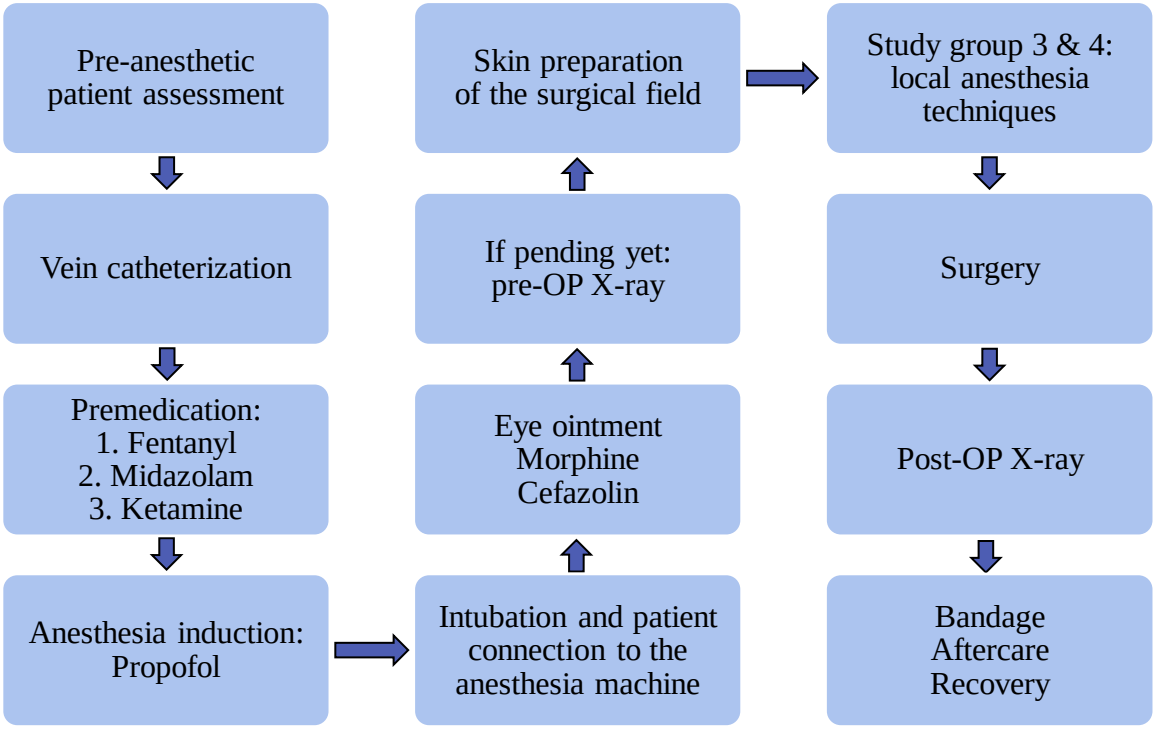


Figure 9: Overview of the actions carried out in the perioperative period

3.3.1 Actions during the preoperative period

Feed was withheld from all dogs for approximately 12 hours prior to arrival at the clinic, while water was provided with free access. At the surgery preparation area, first the dogs underwent a brief pre-anesthetic assessment and clinical examination with special attention spent to the hydration status, respiratory and cardiovascular system. In certain cases, for instance in geriatric patients or in the presence of any signs which might represent underlying diseases, laboratory tests or diagnostic imaging techniques (X-ray, echocardiography and abdominal ultrasound) were performed additionally.

If the dogs, based on those findings, were judged to be able to undergo the anesthesia and the surgery, all required drugs and equipment (e. g. endotracheal tube and anesthesia machine) were prepared to be ready to use to be able to react immediately in case of any emergency situations.

Then, a skin-window on the forelimb was clipped via atraumatic clipper and aseptically prepared *[Bradoderm Soft surgical hand and skin disinfectant 1000 ml]* for the vein catheterization. A vein catheter of appropriate size was placed into the cephalic vein and the dogs were premedicated by consecutive intravenous application of Fentanyl, Midazolam and Ketamine. General anesthesia was induced via slow intravenous administration of Propofol. The applied dose were estimated based on effect, due to evaluation of the general muscle tone, jaw tone, palpebral reflex and swallowing reflex.

The unconscious patients were intubated orotracheal with an endotracheal tube of appropriate size. After fixation of the endotracheal tube and inflation of its cuff, the animals were connected to the anesthesia machine. Within the surgery preparation area, the patients' anesthesia was maintained via Isoflurane delivered in O_2 via a fresh flow rate of 1,8 – 2 l/min, using a partial rebreathing circuit. Unless manual ventilation was necessary, the dogs were on spontaneous respiration.

Moisturizing eye gel *[Bausch + Lomb Corneregel 5 % Dexpanthenol eye gel 10 g]* was applied onto the cornea to protect it from dehydration. Preoperative antibiotic prophylaxis was provided by intravenous administration of Cefazolin. Morphine, which was part of the multimodal analgesic protocol in each group, was injected intramuscularly.

Unless it has been done before, the patients were transferred to the radiology department for taking the preoperative X-rays which are obligatory for performing the surgery. During this short period of time, the general anesthesia was maintained by the use of Propofol.

Back into the surgery preparation area, the dogs again were connected to the anesthesia machine and the surgical field and its extended adjacent area was prepared via atraumatic hair clipping and disinfecting skin washing using antimicrobial liquid hospital soap *[Bradonett disinfecting liquid soap 5 l].*

3.3.1.1 Study protocol 3

In the study groups 1 and 2, no additional local anesthesia techniques were performed.

Following the general preparation for the surgery, the dogs of study group 3 received the local femoral nerve anesthesia. While the patients were placed in lateral recumbency, laying on the healthy limb and the hindlimb to be operated was lifted up to provide access to its medial surface, the previously clipped and washed skin *[Bradonett disinfecting liquid soap 5 l]* at the region of the femoral triangle was aseptically prepared by the use of surgical skin disinfectant solution *[Bradoderm Soft surgical hand and skin disinfectant 1000 ml].* Figure 10 illustrates the site of injection for the local femoral nerve anesthesia.

The femoral nerve exits the femoral canal and travels cranially to the femoral artery and quite superficial into distal direction [14]. To target the nerve, the femoral artery was palpated close to the inguinal region and a needle (23 G) connected to the Lidocaine-filled syringe was inserted caudally of the sartorius muscle and cranially of the femoral artery, with an angle of 20 – 30 ° and approximately 1 – 1,5 cm deep into the tissue. After aspiration to verify the correct needle position, a volume of approximately 0,5 – 1,5 ml (depending on the size of the dog and the volume necessary to be given) was injected perineurally. This application was repeated along the nerve while slightly moving into distal direction to divide the total volume of Lidocaine into several perineural injections (3 – 5). The whole procedure was performed under strict aseptic conditions.

By this technique, it may happen that the saphenous branch will be blocked only. It depends on how proximal the needle was inserted and the individual variation of nerve branching as well as the distribution of the drug [14].

3.3.1.2 Study protocol 4

The dogs which have participated in the protocol of study group 4, before being transferred into the operation theatre, received the intra-articular stifle joint anesthesia combined with the sciatic nerve and femoral nerve block.

For the arthrocentesis, the dogs were placed in lateral recumbency and the hindlimb to be operated was lifted and held in a slightly flexed position by an assistant. The clipped and washed skin *[Bradonett disinfecting liquid soap 5 l]* covering the stifle joint was triple-repetitive aseptically prepared *[Bradoderm Soft surgical hand and skin disinfectant 1000 ml]* and exclusively sterile equipment (gloves, needles and syringes) was used.
The patella, patellar ligament and tibial tuberosity served as landmarks to target the lateral stifle joint recess. Digital pressure was applied on the medial recess and the lateral recess was punctured at the midpoint between an imaginary line connecting the patella and the tibial tuberosity. A needle (22 G) connected to an empty syringe (2 ml) was inserted and directed carefully towards the central intercondylar area of the joint cavity. Aspiration was necessary for confirmation of the correct needle positioning. In some cases, due to local inflammatory processes, the synovia was characterized by a mild macroscopic hemorrhagic infiltration. Following successful arthrocentesis, the syringe was disconnected from the needle and the previously sterile prepared Lidocaine was injected intra-articularly. After needle and syringe removal, digital pressure was applied on the site of punctuation and the joint was manually flexed and extended to provide equal drug distribution between the communicating stifle joint recesses.

The thick sciatic nerve passes the caudal border the femur's greater trochanter and from there travels into distal direction, embedded between the biceps femoris muscle (laterally) and the semimembranosus muscle (caudomedially) [42]. When the dog is placed in lateral recumbency with the healthy leg facing upwards, the sciatic nerve can be targeted by a lateral approach at the level of the coxofemoral joint, where the nerve lies quite superficial and does not yet bifurcate into the tibial nerve and peroneal nerve [14]. Figure 11 shows the site of injection for the local sciatic nerve anesthesia.
For the nerve anesthesia, the clipped and washed skin *[Bradonett disinfecting liquid soap 5 l]* covering the area around the coxofemoral joint was aseptically prepared *[Bradoderm Soft surgical hand and skin disinfectant 1000 ml]* and an imaginary horizontal line was drawn

between the greater trochanter and the ischial tuberosity. At one third distance from the first landmark, a needle (23 G) connected to the drug-filled syringe was inserted approximately 1,5 – 2 cm deep through the skin and directed slightly cranially. After aspiration to avoid an intravascular application, the Lidocaine-Bupivacaine anesthetic mixture was injected perineurally. The total volume was distributed evenly into several perineural injections, each of 0,5 – 1,5 ml. Just like it was done in the femoral nerve block, the sciatic nerve block was carried out under strict aseptic conditions as well.

The femoral nerve block was performed in the same way as described for the patients which underwent the surgery within protocol 3. The only difference was that the Lidocaine-Bupivacaine mixture was used.

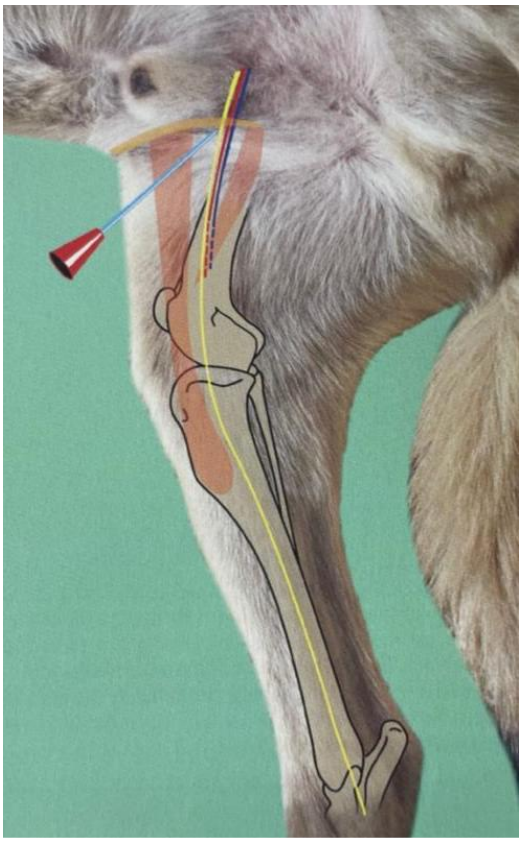


Figure 10: Local femoral nerve block

The femoral nerve can be targeted on the medial site of the hindlimb, close to the inguinal region and cranially of the femoral artery.

(Figure taken from [42 p 152])

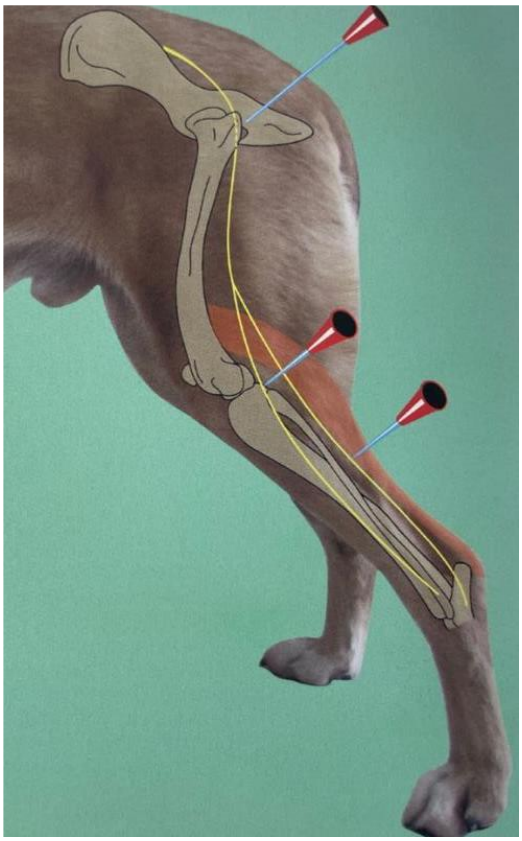


Figure 11: Local sciatic nerve block

The sciatic nerve is blocked from a lateral approach, caudally of the femur's greater trochanter at the height of the ischial tuberosity.

(Figure taken from [42 p 152])

3.3.2 Actions during the intraoperative period

3.3.2.1 Arrival at the operation theatre

Following completion of the described steps of patient preparation, the dogs were transferred into the operation theatre, where they were placed into a soft positioning pillow covered by an heating pad to provide a stable dorsal recumbency and to counteract hypothermia. The hindlimb to be operated was slightly extended into caudal direction and triple-repetitive aseptically prepared via surgical skin disinfectant solution *[Bradoderm Soft surgical hand and skin disinfectant 1000 ml].*

Meanwhile, the patients were connected to the *Dräger Primus anesthesia machine*, the monitoring equipment and the mentioned intravenous infusions.

The *Dräger Primus anesthesia machine* is an unidirectional semi-closed circuit, equipped with a reservoir bag and a carbon dioxide (CO_2) absorber and thereby enables rebreathing. The rate of the rebreathed gas fraction depends on the setting of the fresh gas flow. For partial utilizing of the rebreathing circuit, the O_2 fresh gas flow rate was set to 1,8 l/min and the O_2 concentration was set to 80 %. Due to this, only a small portion of CO_2-extracted gas was rebreathed, while the surplus of oxygen-anesthetic mixture was eliminated continuously via the adjustable pressure limit (APL) valve into the scavenging system. Consequently, the system and the patients' tissues were purged from nitrogen-containing air and simultaneously filled with fresh oxygen-volatile anesthetic agent mixture. This method is beneficial, especially in the initial phase after anesthesia induction, since it allows rapid stabilization of the anesthesia depth [43, 44].

All dogs were ventilated mechanically by means of the machine's volume controlled ventilation mode. For this purpose, the tidal volume (10 – 15 ml/kg BW) and the respiratory rate (9 – 15 / min) were adjusted to maintain a target end-tidal CO_2 concentration of 35 – 45 mmHg and a target peak inspiratory airway pressure of 10 – 15 cm H_2O. To prevent a high pressure limit-caused alveolar barotrauma, the pressure limit was set to 20 mbar, which is equal to 20 cm H_2O.

General anesthesia was maintained inhalational via Isoflurane delivered in O_2. The vaporizer was adjusted individually to inspiratory Isoflurane concentrations which were appropriate to ensure a sufficient depth of anesthesia (1,4 – 2,2 %).

3.3.2.2 Surgical procedure

The first skin incision in average was performed 47 minutes after anesthesia induction. Thus, the surgery started with an exploratory microarthrotomy for removal of the CrCL remnant and investigation of the menisci, especially the caudal pole of the medial meniscus, for the presence of any injuries. If indicated, a partial meniscectomy, depending on the severity of the lesion, was performed. After flushing the joint cavity with sterile isotonic NaCl solution *[NaCl 0,9 % B. Braun Ecolav sterile irrigation solution 100 ml],* the joint capsule was closed via continuous suture pattern using synthetic absorbable monofilament suture material composed of polydioxanone *[Vetsuture PDX USP 0].*

This procedure was followed by the actual steps of the TPLO. As mentioned before, to be able to neutralize the cranial tibial thrust and thereby regaining the joint's stability, the physiological slope of the TP has to be diminished via rotation of the tibial condyle into caudal direction. The dogs' preoperative TPA was measured on the previously taken mediolateral X-ray. Based on this and the radius size of the chosen sawblade, the dimension of rotation of the TP, expressed in mm, necessary to neutralize the cranial tibial thrust was determined. The target was to achieve a postoperative TPA of 0 °.

Prerequisites for the tibial osteotomy were the soft tissue dissection and preparation on the medial surface of the proximal part of the tibia as well as identifying the appropriate area for place in position the sawblade. Then, initially a partial osteotomy was performed, to be able to set two markings along the semicircular saw line into the tibial bone, with a distance to each other equal to the required rotation of the tibial condyle (in mm). Thereafter, the tibial osteotomy was completed and a rotatory pin was inserted into the now disconnected tibial condyle to be able to handle it. The tibial condyle bone segment was rotated into caudal direction until both bone markings met each other and were fused to one line. At this point, a temporary Kirschner wire was placed through the tibial tuberosity to maintain the new bone configuration. The rotatory pin was removed and a TPLO bone plate of appropriate size was implanted via 6 screws to fix the new alignment of the tibia. At the end of the procedure, the temporary Kirschner wire was removed.

Closure of the wound was achieved via simple continuous suture pattern on the fascia and subcutis using *Vetsuture PDX USP 0* suture material, followed by intracutaneous suture using *Vetsuture PDX USP 2/0* suture material and finally Ford interlocking pattern on the skin. The overall average surgery time was 67 minutes from the first skin incision until completion of the skin closure.

3.3.3 Intraoperative monitoring

3.3.3.1 General intraoperative monitoring

The dogs' vital parameters and depth of general anesthesia were continuously monitored during the entire intraoperative period. Estimation of the depth of general anesthesia was made based on assessment of the general muscle tone, jaw tone, reflexes (e. g. swallowing and palpebral reflex), the size of the pupils, bulbus direction and changes in respiratory pattern as well as in the HF. Consequently, beside using the mechanical monitoring equipment, the integration of the own human senses (palpation, auscultation and inspection) was an essential part of the patient monitoring, also to be able to reliably identify artefactual information given by the monitors.

The following parameters were taken at close intervals and were recorded in the patients' anesthesia protocols: O_2 fresh flow rate (l/min), delivered O_2 gas concentration (%), Isoflurane concentration (V%), peripheral O_2 saturation (SpO_2 in %), end-tidal CO_2 concentration ($etCO_2$ in mmHg), respiratory rate (per minute), HF (per minute), systolic / diastolic / mean arterial blood pressure (NiBP in mmHg), esophageal temperature (° C), color of the mucous membranes and capillary refill time (CRT in seconds).

By means of the use of the *Dräger Vista 120S multiparametric monitor*, all the below described parameters were continuously monitored and recorded.
Both the O_2 saturation of hemoglobin in the arterial blood (SpO_2) and the pulse rate (PR) were measured continuously via placement of the pulse oximeter's sensor onto the dogs' tongue. Furthermore, the pulse oximeter has provided a graphical demonstration of the arterial perfusion at the probe's site, which was converted into the photoplethysmograph (Pleth). The heart rate (HR) and the cardiac cycles were recorded by the use of an Einthoven two-lead system electrocardiographic device. Based on the oscillometry principle, the systolic, diastolic and mean arterial blood pressure values (NiBP) were detected non-invasively. For that purpose, the antebrachium was equipped with an appropriate-sized cuff which has measured the arterial blood pressure periodically automatic as well as manually targeted. An esophageal thermometer was inserted oropharyngeal for determination of the dogs' internal body temperature (TEMP).

The display of the *Dräger Primus anesthesia machine* has provided further information.
A sidestream capnograph was used to measure the inspiratory ($inCO_2$) and end-tidal CO_2 ($etCO_2$) partial pressure levels. In relation to those, the capnogram graphically has reflected the four phases of the respiratory cycle. Certain tiny and irregular alterations of the normally nice and regular capnogram's shape may be early indicators for severe nociceptive stimulation, inasmuch the dog may escape the mechanical ventilation and may start falling into a shallow panting-like respiratory pattern.
Moreover, the anesthesia machine's display has listed the ventilatory volume fractions (minute volume (MV) and tidal volume (V_T)), the respiratory rate (frekv.), the airway pressure conditions (pressure peak at max. inspiration (PEAK), plateau pressure (PLAT) and positive end-expiratory pressure (PEEP)) as well as the inspiratory and expiratory O_2 (insp. and exp. O_2) and Isoflurane (insp. and exp. Iso.) concentrations in the system.

3.3.3.2 Evaluation of intraoperative nociception

Special attention was spent on the recognition of signs which have reflected activation of the nociceptive pathway. Consequently, any changes in response to surgical stimulations were recorded. Nociceptive perception predominantly was assumed based on rise in cardiovascular parameters and changes in respiratory pattern. Important to mention is that such changes also may be the consequence of a superficial anesthesia depth or certain pathologic conditions.
A compensatory tachycardia for instance develops in case of anemia, hypoxemia, hypovolemia (fluid deficit or blood loss) or vasodilation (anaphylaxis or drug-induced side effects) leading to hypotension. Examples of further underlying causes of canine tachycardia are tachyarrhythmias and hormone producing thyroid tumors.
Potential underlying pathologic conditions of canine hypertension are kidney diseases, hypercortisolism (Cushing syndrome), hyperaldosteronism (Conn's syndrome) or increased intracranial pressure conditions (e. g. brain tumor). A general prominent sympathetic tone may be the consequence of a pheochromocytoma.
Therefore, the patients' pre-anesthetic examination and intraoperative polyparametric assessment in addition to the interconnection to current surgical manipulations is crucial to avoid misinterpretation of the findings.

If the HF or SAP or both, as response to current surgical stimulation, were increased by approximately ≥ 15 % from the previously recorded baseline value, a Fentanyl rescue analgesia bolus *(approximately 0,5 µg/kg BW IV)* was administered intravenously.

3.3.4 Actions during the postoperative period

After completion of the surgery, the dogs were introduced back into spontaneous respiration to be able to disconnect them safely from the *Dräger Primus anesthesia machine*. The surgical field was cleaned from blood and the suture line was covered using a gauze swab and a plaster as a simple dressing. Maintained by Propofol, the anesthetized patients were transferred into the radiology department for taking the postoperative X-rays.

Thereafter, they were carried back into the surgery preparation area, where the anesthesia was maintained inhalational via Isoflurane (1 – 1,5 %) on a depth sufficient to be able to apply a Modified Robert Jones Bandage to the operated limb. This bandage stayed for maximal 2 days with the main purpose of providing compression and thereby preventing edema formation. Furthermore, the bandage has protected the suture line from licking.

The Isoflurane administration then was stopped and the dogs were closely observed until extubation was indicated. Heating sources, such as a heating pad and an active warm air blanket system were used for rewarming of hypothermic patients. The overall anesthesia time in average was 150 minutes.

After regain of consciousness, Meloxicam was injected subcutaneously and the body temperature as well as the behavior (e. g. post-anesthesia excitement and expression of pain) were regularly re-checked during the period of recovery.

The dogs could been discharged from the clinic when they were in a stabile hemodynamic condition and when they were able to stand up and move on their own, which took approximately 1,5 – 3 hours of recovery. Prior to their clinic discharge, the vein catheter was removed and replaced by a temporary slightly pressure-causing bandage.

4 RESULTS

4.1 Patient demographics

Data from 60 operated dogs are included in the final analysis, which will be discussed in the following.

5 % of the dogs had the TPLO surgery combined with the surgical correction of a medially directed patellar luxation. Among all patients, one dog had septic arthritis and synovitis (Serratia marcescens) in the diseased stifle joint prior to the surgery. This condition was treated first and the TPLO surgery was performed four weeks later. One other dog was laboratory confirmed as being infected with Methicillin-resistant Staphylococcus pseudointermedius (MRSP).

The general patient demographics and procedural data are summarized in Table 2. Figure 12 illustrates the detailed breed distribution, while Figure 13 shows the detailed age distribution.

Table 2: Patient demographics and procedural data

	Study group/ protocol 1	**Study group/ protocol 2**	**Study group/ protocol 3**	**Study group/ protocol 4**	**Overall**
Dogs (total number)	18	17	18	7	60
Concurrent patellar luxation (%)	0	6	11	0	5
Females (%)	56	71	61	86	65
intact (%)	20	33	45	50	36
spayed (%)	80	67	55	50	64
Males (%)	44	29	39	14	35
intact (%)	88,5	60	86	100	81
castrated (%)	12,5	40	14	0	19
*BW (kg)**	27,3 (13 – 45,6)	22,9 (8,8 – 55)	31,4 (17,5 – 55,4)	25 (20 – 30,6)	27 (8,8 – 55,4)
*Age (years)**	9 (2 – 12)	6 (1 – 11)	6 (2 – 10)	8 (3 – 11)	7 (1 – 12)
ASA 1 (%)	6	29,4	28	43	23
ASA 2 (%)	22	29,4	33	14	27
ASA 3 (%)	28	11,8	39	29	27
ASA 4 (%)	44	29,4	0	14	23
*Anesthesia time (min)**	144 (110 – 170)	143 (115 – 185)	159 (105 – 220)	156 (122 – 175)	150 (105 – 220)
*Surgery time (min)**	67 (45 – 83)	68 (40 – 117)	69 (42 – 98)	55 (42 – 66)	67 (40 – 117)
*Time from induction until surgery start (min)**	42 (30 – 52)	42 (25 – 64)	51 (33 – 67)	64 (45 – 82)	47 (25 – 82)

* = mean (minimum – maximum)

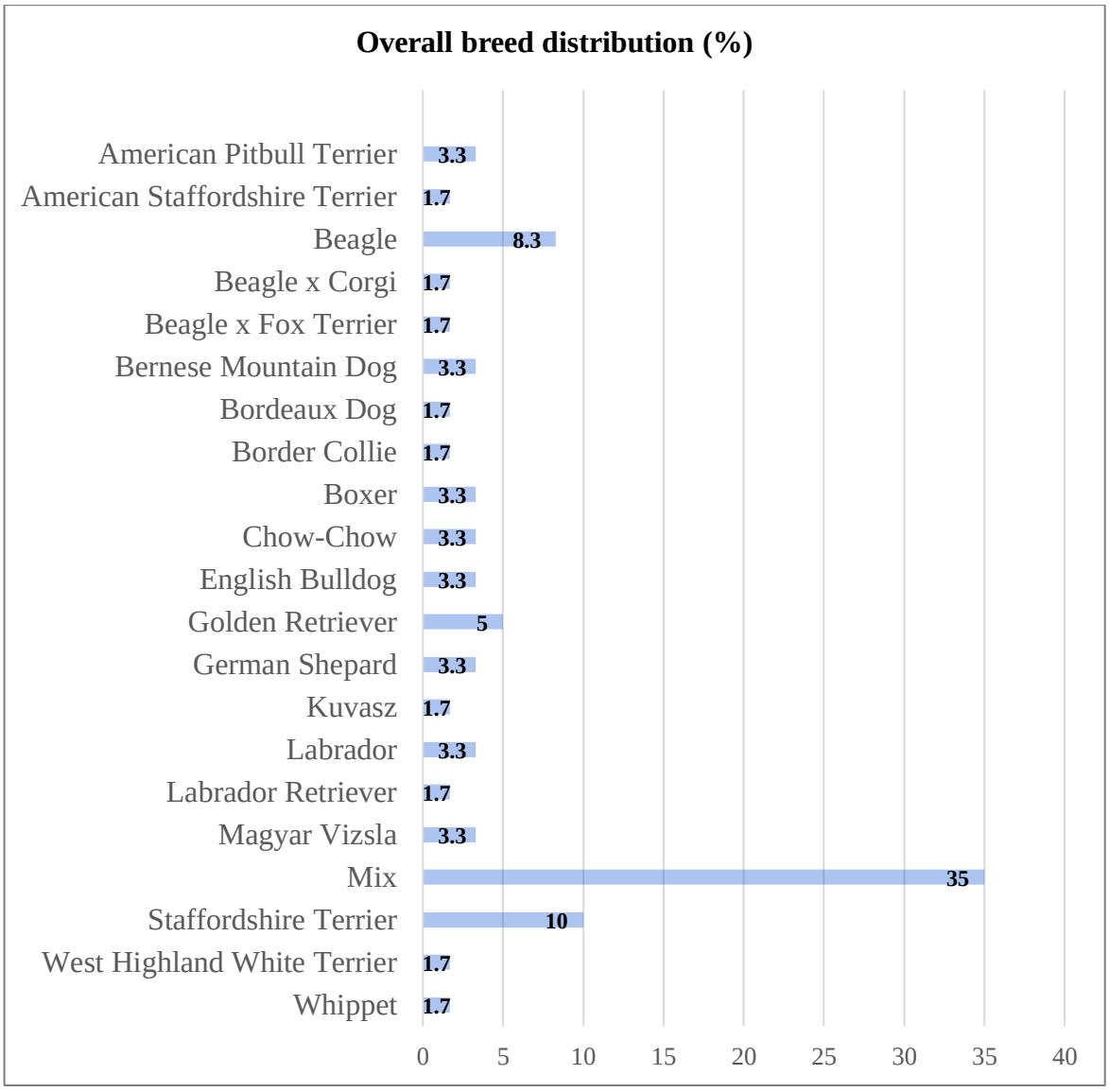


Figure 12: Overall breed distribution (%)

The dogs participating in the study had a range of various predominantly large breeds, such as American Staffordshire Terrier, Bernese Mountain Dog, Boxer, Bulldog, Chow-Chow, Labrador and Labrador Retriever, which are listed as typical high-risk breeds by several authors [1, 2, 8, 16]. Interestingly, Beagles (purebred and mixed) have been operated in the same quantity as (American) Staffordshire Terriers (both breeds in total of 11,7 %). Nevertheless, most of the operated dogs were mixed breeds (35 %). The mean body weight was 27 kg, whereas the lowest body weight was 8,8 kg and the highest body weight was 55,4 kg.

Regarding the sex distribution, 65 % of the dogs were females, from which 36 % were intact and 64 % were spayed. From the 35 % male dogs, 81 % were intact and merely 19 % were neutered. These numbers therefore corroborate the hypothesis that female dogs are affected by the CrCLD with a higher incidence compared to the male ones. It also can be said that a castration may elevate the risk in females. However, in this study, this could not be proven for the male individuals.

The patients' age ranged from 1 – 12 years, with a mean age of 7 years. Figure 13 shows well that the range of age with the highest incidence was 10 – 11 years, followed by the second highest incidence age which was 2 years. In consideration with the fact that the cases most likely have developed according to the chronic degenerative pathogenesis, the high incidence in such a young age emphasizes that underlying risk factors (e. g. genetic predispositions) very likely tend to play a central role.

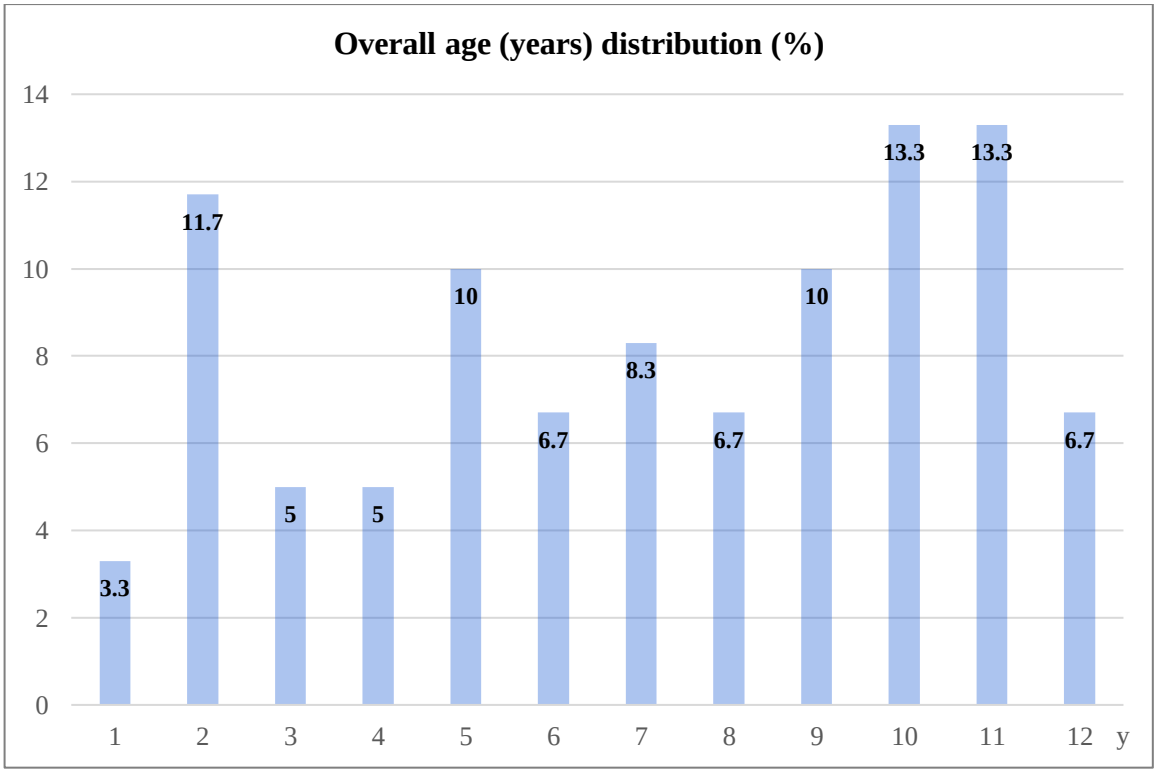


Figure 13: Overall age distribution (%)

4.2 Comparative monitoring

Table 3 provides a comparative overview of the recorded HF, SAP and Isoflurane concentrations.

Table 3: Summarized intraoperative monitoring of the HF, SAP and Isoflurane conc.

Intraoperative monitoring

a. Study group / protocol 1

	HF (bpm)*	SAP (mmHg)*	Isoflurane conc. (%)*
Skin preparation	123 (87 – 166)	Ø	2,0 (2,0 – 2,1)
Surgery start	105 (73 – 150)	94 (68 – 130)	1,9 (1,5 – 2,0)
Microarthrotomy	122 (62 – 170)	115 (90 – 135)	1,9 (1,7 – 2,0)
Lig. remnant removal	85 (49 – 138)	114 (82 – 138)	1,8 (1,5 – 2,0)
Partial meniscectomy	86 (64 – 125)	111 (80 – 135)	1,8 (1,4 – 2,0)
Tibial osteotomy	116 (80 – 160)	117 (84 – 135)	1,8 (1,5 – 2,0)
Drilling	106 (82 – 130)	114 (80 – 135)	1,8 (1,6 – 2,0)
Wound closure	97 (69 – 125)	113 (84 – 135)	1,8 (1,4 – 2,0)

b. Study group / protocol 2

	HF (bpm)*	SAP (mmHg)*	Isoflurane conc. (%)*
Skin preparation	111 (53 – 150)	Ø	2,0 (1,4 – 2,0)
Surgery start	90 (53 – 145)	93 (60 – 129)	1,8 (1,4 – 2,2)
Microarthrotomy	112 (52 – 160)	108 (73 – 133)	1,8 (1,4 – 2,1)
Lig. remnant removal	93 (62 – 172)	113 (73 – 134)	1,8 (1,5 – 2,1)
Partial meniscectomy	95 (70 – 155)	121 (109 – 134)	1,9 (1,6 – 2,1)
Tibial osteotomy	110 (76 – 170)	118 (89 – 135)	1,8 (1,5 – 1,9)
Drilling	102 (71 – 138)	117 (89 – 135)	1,7 (1,5 – 2,0)
Wound closure	105 (80 – 164)	111 (82 – 130)	1,8 (1,4 – 2,1)

c. Study group / protocol 3

	HF (bpm)*	SAP (mmHg)*	Isoflurane conc. (%)*
Skin preparation	105 (60 – 190)	Ø	2,0 (1,7 – 2,0)
Surgery start	91 (52 – 120)	86 (65 – 107)	1,8 (1,6 – 1,9)
Microarthrotomy	113 (78 – 180)	106 (80 – 135)	1,8 (1,6 – 1,9)
Lig. remnant removal	86 (62 – 112)	108 (76 – 134)	1,8 (1,7 – 2,0)
Partial meniscectomy	88 (58 – 130)	104 (89 – 116)	1,8 (1,7 – 1,9)
Tibial osteotomy	113 (73 – 180)	116 (94 – 133)	1,8 (1,7 – 1,9)
Drilling	101 (61 – 135)	114 (84 – 135)	1,8 (1,7 – 1,9)
Wound closure	98 (67 – 126)	107 (89 – 128)	1,8 (1,7 – 2,0)

d. Study group / protocol 4

	HF (bpm)*	SAP (mmHg)*	Isoflurane conc. (%)*
Skin preparation	108 (58 – 180)	Ø	2,0 (2,0 – 2,0)
Surgery start	88 (65 – 111)	87 (69 – 110)	1,7 (1,6 – 1,8)
Microarthrotomy	92 (66 – 123)	98 (75 – 115)	1,8 (1,8 – 1,8)
Lig. remnant removal	85 (66 – 123)	104 (72 – 122)	1,8 (1,8 – 1,8)
Partial meniscectomy	81 (70 – 96)	94 (76 – 116)	1,8 (1,6 – 1,8)
Tibial osteotomy	98 (80 – 130)	109 (84 – 125)	1,7 (1,6 – 1,8)
Drilling	81 (76 – 87)	100 (73 – 115)	1,7 (1,5 – 1,8)
Wound closure	79 (67 – 101)	99 (83 – 122)	1,7 (1,6 – 1,8)

HF = heart frequency (bpm)
SAP = systolic arterial blood pressure (mmHg)
* = mean (minimum – maximum)

4.3 Intraoperative nociception

4.3.1 Indicators and severity of intraoperative nociception

The microarthrotomy and tibial osteotomy clearly were identified as the surgical actions where the most severe nociceptive provocation has originated. However, beside those, also the manipulations within the joint cavity (CrCL remnant removal and partial meniscectomy), the joint capsule suturing, soft tissue preparation for the TPLO and drilling into the tibial bone in some patients could have been associated with acute activation of the nociceptive pathway. This assessment was made based on evaluation of the recorded respiratory and cardiovascular parameters.

Table 4 summarizes changes in respiratory pattern. Additionally, to be able to evaluate and compare the severity of current nociceptive signal transmission, the percentage elevation of the HF and the SAP in relation to the previously recorded baseline value was calculated. This is shown in Table 5.

Table 4: Summary of the respiratory pattern in correlation to the surgical manipulations

Patients (%) which switched into transient panting-like respiratory pattern				
	Study group 1	**Study group 2**	**Study group 3**	**Study group 4**
Microarthrotomy	17	0	11	0
Lig. remnant removal	0	0	6	0
Partial meniscectomy	0	0	0	0
Joint capsule suturing	0	0	6	0
Preparation TPLO	0	6	0	0
Tibial osteotomy	0	0	22	0
Drilling	6	6	22	0

Some dogs (6 – 22 %) which were distributed within the first three study groups escaped the mechanical ventilation during drilling into the tibial bone. Additionally, the microarthrotomy has caused nociceptive-induced panting-like respiratory pattern in some patients in the first and third study group (11 – 17 %).

Individuals form the third study group, during certain surgical actions (tibial osteotomy, drilling > microarthrotomy > CrCL remnant removal, joint capsule suturing), due to severe nociceptive experience, most significantly have switched into transient panting.

In contrast to those findings, no patient among study group 4 has ever escaped the mechanical ventilation.

Table 5: Summarized changes in HF and SAP in correlation to the surgical manipulations

a. Patients (%) which had an elevation in the HF

	Study group 1	Study group 2	Study group 3	Study group 4
Microarthrotomy	83	88	78	57
Lig. remnant removal	17	41	33	14
Partial meniscectomy	50	41	44	14
Joint capsule suturing	22	59	44	43
Preparation TPLO	17	47	83	86
Tibial osteotomy	100	100	100	100
Drilling	72	88	94	86

a.1 Severity of the parametric elevation of the dogs indicated in Table a
Elevation in the HF from baseline value (%)*

	Study group 1	Study group 2	Study group 3	Study group 4
Microarthrotomy	31 (5 – 108)	46 (7 – 126)	36 (4 – 115)	15 (6 – 35)
Lig. remnant removal	15 (5 – 25)	38 (6 – 71)	15 (4 – 34)	6 (6 – 6)
Partial meniscectomy	16 (4 – 47)	26 (4 – 82)	32 (4 – 100)	16 (16 – 16)
Joint capsule suturing	11 (8 – 13)	17 (6 – 32)	31 (9 – 76)	6 (6 – 7)
Preparation TPLO	21 (4 – 48)	22 (5 – 63)	22 (4 – 51)	8 (5 – 12)
Tibial osteotomy	21 (4 – 40)	28 (7 – 50)	41 (15 – 122)	27 (5 – 91)
Drilling	15 (3 – 37)	26 (2 – 109)	16 (3 – 33)	10 (4 – 20)

b. Patients (%) which had an elevation in the SAP

	Study group 1	Study group 2	Study group 3	Study group 4
Microarthrotomy	83	71	78	57
Lig. remnant removal	11	47	34	14
Partial meniscectomy	17	18	17	14
Joint capsule suturing	0	6	11	14
Preparation TPLO	11	24	44	29
Tibial osteotomy	89	59	89	86
Drilling	28	47	39	43

b.1 Severity of the parametric elevation of the dogs indicated in Table b
Elevation in the SAP from baseline value (%)*

	Study group 1	Study group 2	Study group 3	Study group 4
Microarthrotomy	34 (18 – 63)	27 (2 – 59)	28 (12 – 60)	19 (9 – 32)
Lig. remnant removal	17 (10 – 23)	15 (2 – 47)	17 (6 – 32)	16 (16 – 16)
Partial meniscectomy	8 (3 – 16)	25 (5 – 63)	8 (3 – 15)	5 (5 – 5)
Joint capsule suturing	Ø	11 (11 – 11)	21 (7 – 34)	11 (11 – 11)
Preparation TPLO	6 (1 – 11)	9 (2 – 15)	11 (2 – 26)	8 (5 – 10)
Tibial osteotomy	9 (2 – 19)	9 (1 – 26)	11 (2 – 21)	10 (3 – 16)
Drilling	8 (3 – 17)	13 (3 – 31)	9 (2 – 18)	10 (9 – 10)

* mean (minimum – maximum)

An increase in HF during the **tibial osteotomy** was detected in all 60 participating dogs. However, this was the most severe in the dogs belonging to group 3, which exclusively received the femoral nerve block without pre-emptive analgesia boluses. In those patients, the mean elevation in HF from the baseline value was 41 % and the maximum elevation was 122 %. In contrast to those, the mean elevations in the other three groups were between 21 % and 28 %.

More than 75 % of the individuals among the first three groups have reacted with a rise in HF during the **microarthrotomy**. The calculated mean elevations from the baseline values had a range between 31 % and 46 %. Very severe maximum elevations of more than 100 % (108 – 126 %) were recorded in each of the three groups. Contrary to that, just in 57 % of the dogs among group 4, which received the intraarticular anesthesia and both local nerve blocks, HF elevations were detected during the microarthrotomy. In those individuals, the severity was significantly lower and in most of the cases no indication for a Fentanyl rescue analgesia bolus. Hence, the calculated percentage elevation values (mean 15 %, maximum 35 %) were less than the half compared to those which were calculated for the first three groups.

During the **partial meniscectomy**, more than 40 % of the dogs in each of the first three groups have reacted with elevations in the HF, from which the dogs of the third group had the highest elevations (mean 32 %, maximum 100 %). From group 4 merely 14 % have responded to the manipulations within the joint cavity with a rise in HF. Among those patients, the mean elevation during the CrCL remnant removal was 6 % and the mean elevation during the partial meniscectomy was 16 %.

In General and compared to the other groups, the average increase in HF from the baseline value in group 4 was calculated as the mildest during all surgical actions ($\leq$ 16 %). The only exception for this was the tibial osteotomy, where the patients from group 4 had the second least average rise in HF (27 %) after the least average rise which was recorded in group 1 (21 %).

According to the SAP, the **microarthrotomy** was the leading event which has caused an increase in all four study groups. In the dogs among the first three groups, more than 70 % had mean elevations of 27 – 34 % from the baseline values, while only 57 % of the dogs from the fourth protocol had mean elevations of merely 19 %.
In regard to the individuals which underwent the surgery within protocol 3, almost half of the dogs had an increase in SAP during the **soft tissue preparation** for the TPLO (44 %). Furthermore, those dogs had the most severe mean rise in SAP during **suturing of the joint capsule** (21 %).
Beside those findings, only minor differences related to changes in SAP were recorded within the four study groups.

Some dogs within the study have presented with very prominent sensitivity also to non-invasive manipulations which have affected the diseased stifle joint. 8,3 % of all patients have reacted very sensitive to digital stifle joint manipulation (palpation and flexion). This was detected during the skin preparation (hair clipping and aseptic skin preparation), so even before the start of the surgery. Any following surgical manipulations (arthrotomy, osteotomy and drilling) have provoked huge parametric elevations and were quite difficult to control. This phenomenon promotes the hypothesis that certain mechanisms may modify the sensitivity to incoming nociceptive stimuli (e. g. peripheral and central sensitization processes).

4.3.2 Antinociceptive management via the use of Fentanyl

Fentanyl was the first drug of choice to treat the activated nociceptive pathway. In the study groups 1 and 2, Fentanyl was given as pre-emptive boluses, approximately 2 – 3 minutes prior to the crucial surgical manipulations. In contrast to that, in the study groups 3 and 4, Fentanyl was given in form of rescue boluses only.

The decision making of intraoperative Fentanyl application always has included an adequate general monitoring of the patients' hemodynamic state, vital parameters and depth of general anesthesia to avoid misinterpretation of any parametric abnormalities and/or changes. Also important was the interconnection to current surgical actions. Table 6 summarizes all intraoperative Fentanyl bolus applications.

Table 6: Intraoperative Fentanyl boluses

	Administered intraoperative Fentanyl boluses			
	Study group 1	**Study group 2**	**Study group 3**	**Study group 4**
Dogs (%) which received boluses	100	100	89	29
*Nr. of given boluses per patient in total	4 (1 – 8)	4 (1 – 8)	3 (1 – 9)	2 (1 – 3)
*Administered bolus dose per patient in total (µg/kg BW IV)	1,9 (0,5 – 4,6)	2,4 (0,6 – 5,2)	1,7 (0,5 – 4,3)	1 (0,6 – 1,4)

* = referring to the dogs indicated in the first row, mean (minimum – maximum)

To evaluate the efficacy of the pre-emptive Fentanyl boluses, the severity of the parametric elevation was investigated. Since the dogs within study group 3 in average had the most severe elevations in HF during the partial meniscectomy, joint capsule suturing, soft tissue preparation for the TPLO and tibial osteotomy, it can be said that the pre-emptive Fentanyl bolus administration was more successful for the antinociception management than the sole local femoral nerve block. However, the individuals of the study groups 1 and 2 still had prominent elevations in the HF and therefore required additional Fentanyl administrations.

Table 6 shows well that the dogs within the first two study groups have received the same bolus quantities, which have been 4 in average. Nevertheless, the patients of group 2, which were not treated with the Fentanyl-Ketamine CRI, required a higher mean dosage of 2,4 µg/kg BW. The dogs which underwent the surgery within protocol 1 in total received a mean dosage of 1,9 µg/kg BW and the dogs in protocol 3 received a mean dosage of 1,7 µg/kg BW.

Very positive results were recorded in the dogs among study group 4, from which merely 29 % required a Fentanyl rescue bolus. Also the bolus average given number of 2 and the average given dose of 1 µg/kg BW were significantly lower than in the other groups. Therefore, it can be said that the application of the intra-articular stifle joint anesthesia combined with the local sciatic nerve and local femoral nerve anesthesia enables the achievement of an opioid sparing effect.

A few dogs were very sensitive to the surgical manipulations but responded well to Fentanyl for a short period of time, while simultaneously no adverse side effects have occurred. Consequently, prominent fluctuations in the HF were detected according to the manipulations throughout the entire surgery, which necessarily have required drug intervention to control the nociceptive input. High numbers of given Fentanyl boluses (9) and total dosages (5,2 µg/kg BW) were recorded in those dogs. Further Fentanyl boluses beyond such limits are contraindicated, inasmuch they highly would be accompanied by cardiovascular adverse effects and the risk of manifestation of an opioid-induced hyperalgesia.

The antinociceptive management in such patients was quite challenging. Alternative treatment possibilities are the intravenous application of a micro-dose of either Ketamine or Lidocaine. Lidocaine, in this application form, has to be given very slowly and the patients have to be monitored observantly. Additionally, it was helpful to ask the surgeon for a short interruption of the surgery (approximately 2 minutes), to give previously applied Fentanyl time to make its impact and to provide a short period of recovery to the patient.

4.4 Adverse side effects and complications

A prominent side effect was the drop in HF in correlation to previously given Fentanyl, which is shown in Table 7.

The highest bradycardia incidence was detected in the third study group. 33 % of the dogs in this group had a HF below 60 beats per minute (bpm), which has occurred after intraoperative application of ≤ 0,5 µg/kg BW Fentanyl (additional to the 5 µg/kg BW given as premedication). The least incidence of 14 % was seen in study group 4, in which a HF below 60 bpm has developed already before the application of additional Fentanyl boluses.

In the bradycardic dogs among study group 1, the drop in HF developed after intraoperatively applied Fentanyl boluses of 0,7 – 0,8 µg/kg BW, whereas bradycardia in one dog of study group 2 has manifested after the intraoperative application of 3 µg/kg BW. Therefore, there was a prominent variation in the threshold dosage of Fentanyl which was tolerated by the individuals without predominantly causing cardiac depression.

Nevertheless, the following surgical actions in bradycardic patients still have caused transient parametric elevations, which were followed again by a drop in HF and in some cases also a regain of bradycardia. The HF consequently underwent prominent fluctuations during the surgery. A bradycardic state was a contraindication for further Fentanyl bolus applications. This phenomenon was a significant disadvantage among the pre-emptive Fentanyl bolus application technique.

Table 7: Perioperative bradycardia

	Perioperative bradycardia			
	Study group 1	**Study group 2**	**Study group 3**	**Study group 4**
HF 60 – 69 bpm detected in dogs (%) occurred after given Fentanyl dose	17 5* + 2,1 (1,6 – 2,7)**	24 5* + 0,7 (0 – 1,7)**	28 5* + 0,6 (0 – 1,6)**	29 5* + 0,3 (0 – 0,6)**
HF < 60 bpm detected in dogs (%) occurred after given Fentanyl dose	17 5* + 0,8 (0,7 – 0,8)**	18 5* + 1,2 (0 – 3)**	33 5* + 0,1 (0 – 0,5)**	14 5* + 0 (0 – 0)**
Dogs (%) which required an Atropine bolus IV (0,01 mg/kg BW)	6	6	12	0

* = dose administered as premedication (µg/kg BW IV)
** = dose administered as intraoperative bolus (µg/kg BW IV), mean (minimum – maximum)

Further common complications which occurred equally distributed within all four study groups were hypothermia (< 37,5 °C) in 81,7 % of the dogs and post-induction hypotension (SAP < 90 mmHg) which was detected in 63,3 % of the dogs.

One of the patients, prior to premedication, has shown severe salivation and therefore was treated with Maropitant *[Cerenia 10 mg/ml Maropitant citrate solution for injection] (1 mg/kg BW IV).* Further two dogs have presented with prominent salivation combined with huge excitement and panting, which introduced them into an hyperthermic state. From those severely stressed dogs, one dog post-induction has fallen into a suspected shock, accompanied by respiratory depression leading to hypoxemia. Thus, stabilization via respiratory support, O_2 supplementation and Ringer-Lactate shock-infusion *[Ringer-Laktát Fresenius solution for infusion 500 ml] (20 ml/kg BW IV)* was performed.

In two patients a hypotension-caused compensatory tachycardia was onset, which was treated via temporary administration of colloidal infusion *[Fresenius Voluven 6 % HAES infusion 500 ml] (1 – 5 ml/kg BW IV)* or application of Norepinephrine infusion solution *[Sinora Sintetica 1 mg/ml concentrate for infusion (5 – 20 µg/kg BW/min IV)* mixed into *physiological Saline Fresenius solution for infusion 100 ml].*

Prominent idiopathic intraoperative bleeding was detected in two of the operated dogs. Sporadically, transient apnoea following anesthesia induction, leading to hypoxemia and a cyanotic tongue, has occurred.

5 DISCUSSION

According to the objectives of the presented study, the benefits of a Fentanyl-Ketamine CRI and certain local anesthesia techniques as add-ons to the ordinary perioperative analgesic drug protocol were evaluated during the TPLO surgery in dogs. In conclusion, both the administration of a Fentanyl-Ketamine CRI and the implementation of a sole local femoral nerve anesthesia via Lidocaine have revealed as not being significantly advantageous.
In contrast to those findings, the application of an intra-articular stifle joint anesthesia via Lidocaine in combination with a local sciatic nerve and local femoral nerve anesthesia via a Lidocaine-Bupivacaine mixture turned out as being fairly successful.

5.1 Advantages and disadvantages of the protocols

5.1.1 Study protocol 1 and 2

The intravenous application of pre-emptive Fentanyl boluses to counteract the activation of the nociceptive pathway could decrease the severity of the percentage parametric rise to a certain extent. However, a prominent problem was the drop in HF underneath physiological levels, which was onset immediately after a bolus application and which has manifested after individually varying dosages. Consequently, a fluctuating rise and fall in HF and SAP according to the surgical actions was a common presentation. Another crucial factor was the appropriate timing of the bolus applications, which was intended to be performed 2 – 3 minutes prior to the surgical stimulations.
Under the additional application of the Fentanyl-Ketamine CRI, lower Fentanyl bolus dosages have turned out as being effective to control acute nociceptive stimulation. Nevertheless, this technique was not sufficient enough to reduce the quantity of Fentanyl boluses.
The comparison of the overall results within the first two study groups did not shown any significant differences in relation to the opioid sparing effect, adverse side effects and the preventive antinociceptive effectivity. Therefore, neither protocol of these two was advantageous over the other one.

5.1.2 Study protocol 3

The local femoral nerve anesthesia was a quite fast and easily performed technique and the perineural injections in this study were not accompanied by any local adverse reactions. Interestingly, the bradycardia incidence in this group was the highest and its onset was detected after lower Fentanyl dosages compared to the first two groups.

Regarding to the antinociceptive efficacy, the sole femoral nerve block has turned out as being the least effective, since it has result in the most severe cardiovascular parametric elevations, especially during the tibial osteotomy. Additionally, changes in respiratory pattern were detected in the most prominent extent in the patients which underwent the surgery within this protocol.

Intraoperative Fentanyl boluses were given in a little less quantity and dosage compared to the first study group. However, this difference cannot be assessed as being really significant or beneficial.

5.1.3 Study protocol 4

The preoperative patient preparation including the local anesthesia techniques was merely a little bit more time-consuming. All three local anesthesia techniques were fairly practical to perform and there was no need for special equipment. No local adverse side effects have manifested yet. The described low risk for long-term consequences in correlation to the potential cartilage damage caused by Lidocaine cannot be evaluated at this point of time.

Especially the intra-articular anesthesia was characterized by an outstanding antinociceptive efficacy. Consequently, the number of dogs which have reacted to the surgical actions with cardiovascular parametric elevations as well as the percentage rise were significantly lower compared to the other three groups. This was proven for most of the surgical manipulations. Very favorable was the prominent opioid sparing effect. The results indicate well that much less dogs had the need for a rescue Fentanyl bolus and also the given bolus quantity and dosage could have been reduced by approximately the half compared to the first two study groups. Additionally, Isoflurane concentrations could have been reduced and the drop in HF below 60 bpm has occurred in the least percentage incidence among all four study groups. Compared to the mono-use of Lidocaine, the application of the Lidocaine-Bupivacaine mixture furthermore ensures a longer duration of action, which beneficially extends its effects beyond the intraoperative period.

In conclusion it can be said that this protocol was very successful and the most effective out of all four study protocols. This evaluation covers the antinociceptive efficacy, opioid and Isoflurane sparing effects and the manifestation of adverse side effects. However, since much less dogs underwent the surgery within protocol 4, the findings could have been more meaningful if the quantity of proband dogs would have been equal in all four study groups.

5.2 General and final conclusions

In general it can be said that nociceptive stimuli originated by very invasive surgical manipulations, such as the completion of the tibial osteotomy, are quite difficult to control. All of the 60 dogs have shown an increase in the HF during this surgical step. Consequently, no drug, especially when given as mono-treatment, can totally interrupt such nociceptive signal transport. Therefore, it is even more important to ensure an adequate drug protocol on the basis of a multimodal approach, to provide the most possible intraoperative antinociceptive support.

In relation to the findings and the patients' histories it has turned out that very sensitive dogs commonly had a long-lasting history of hindlimb lameness and typical lesions of the DJD have already developed due to the chronic pathologic condition. For instance, in one dog the CrCL remnant in the joint cavity was almost totally absorbed. It is described that molecules released during this process may trigger the deterioration of the secondary osteoarthritis [16]. Osteoarthritic degenerated joints are characterized by accumulation of certain inflammatory factors, such as cytokines, especially IL-1, and degradation enzymes, such as metalloproteases [18]. Finally, these molecules also participate in peripheral sensitization processes and therefore tend to play a leading role in increasing the patients' sensitivity [25, 32]. Interestingly, it has been shown that postoperative wound healing disorders and septic complications tend to develop predominantly in such chronic cases, which also may be linked to high IL-1 levels.

Beside peripheral sensitization processes, also signs of central sensitization processes were detected. Thus, a very sensitive dog concurrently has suffered from severe pelvic osteoarthritis, which may be in relation to such mechanisms.

Another hypothetic statement is that huge preoperative excitement in severely stressed dogs probably may facilitate their sensitivity, which subsequently increases the need for Fentanyl rescue boluses.

5.3 Interconnection to other studies

Other studies also examined the antinociceptive efficacy of certain analgesic protocols during canine orthopedic hindlimb surgeries. In those studies, the major focus was set on the application of an epidural anesthesia (EA) and peripheral nerve blocks (PNB).

A study performed by Caniglia et al. has evaluated the intraoperative antinociception during surgical CrCL or medial patellar luxation repair in dogs. The animals, after premedication and general anesthesia induction, received either a lumbosacral epidural anesthesia (LSEA) or a local sciatic nerve block combined with a local femoral nerve block via a Lidocaine-Bupivacaine mixture in both protocols. Their results indicate that there were no significant differences between both study groups regarding to the quantity and dosage of given Fentanyl rescue boluses, with an administered mean dosage of 2 µg/kg BW. Sevoflurane concentrations below the MAC were sufficient to maintain an adequate depth of general anesthesia in both groups.

Contrary to the suspected expectation, the need for hemodynamic support via anticholinergic and inotropic drugs as well as fluid boluses have been equal in all patients as well. Consequently, PNB were not accompanied by less intraoperative hypotension, which might be explained by relatively low anesthetic drug concentrations and a limited drug spread within the epidural space. One of the dogs which were treated with the PNB postoperatively has presented with sciatic nerve deficits, but those signs completely have resolved within 30 hours. The nociceptive efficacy was assessed as being equal and the study therefore turned out that PNB are effective alternatives to an EA. In confirmation with the findings of our own study, the authors have highlighted that, especially in chronic cases, complex pathogenetic processes are involved in modification mechanisms which tend to affect the patients' nociceptive pathway [45].

Sarotti et al. have examined the outcomes of an EA via Morphine added to Bupivacaine applied at two different injection sites (L7 – S1 and L5 – L6) in dogs during orthopedic hindlimb surgeries. None of the in literature described side effects that may be accompanied by an EA, such as postoperative urinary retention, pruritus or neurological damage were detected. Observed adverse effects in both study groups were hypotension (in 25 % and 37 %) and bradycardia (in 7 % and 11 %). The intraoperative administration of Fentanyl rescue boluses was necessary in 52 % and 30 % of the patients and the given mean dosages were 1 (0 – 3) µg/kg BW and 0 (0 – 2) µg/kg BW [46].

In comparison with our study, these are roughly similar results to those obtained in the dogs within protocol 4. Especially the need for Fentanyl rescue boluses was comparable (rescue bolus administration in 29 % and a mean dosage of 1 (0,6 – 1,4) µg/kg BW). The bradycardia occurrence was in a similar range as well (14 %).
Furthermore, Sarotti et al. have described that postoperative proprioceptive deficits were detected in 12 % and 50 % of the patients after 8 hours. One dog had proprioceptive deficits which have lasted for 24 hours but have resolved completely after 36 hours.
As a general comparative statement, the authors have associated PNBs with a wider acceptance, higher success rates and fewer side effects [46].

Kalamaras et al. in their study have evaluated postoperative analgesic and sedative effects of certain perioperative analgesic protocols in dogs which underwent a TPLO surgery combined with an arthroscopy. Their results show that a sciatic nerve block combined with a saphenous nerve block induced via Ropivacaine has provided the best postoperative analgesia and the least sedation compared with a LSEA and a Morphine-Lidocaine-Ketamine CRI. Subsequently, these PNBs are recommended to get incorporated in standard multimodal analgesic protocols for dogs undergoing TPLO surgery [47].

In advocation to the above mentioned, an electronic survey carried out by Parker et al. revealed that PNBs were the preferred approach compared to a LSEA and a peri-incisional infiltration by the majority of respondent diplomates. In unanimity with the results of our study, a proximal femoral or saphenous nerve block combined with a sciatic nerve block were the most preferred sites for a peripheral nerve anesthesia, whereas the sole femoral nerve block was ranked as the least preferred technique. The most privileged applied drug was Bupivacaine as mono-use, followed by Bupivacaine or Ropivacaine combined with additives (e. g. Dexmedetomidine) or a Bupivacaine-Lidocaine solution as mixed local anesthetic drug. No respondent has recommended Lidocaine in a form of a mono-application.
In relation to the effectivity, there were no huge differences between PNBs and an EA. However, PNBs were associated with the lowest need for rescue analgesia boluses and the least side effects, which in particular means a lower risk for induced hypotension. Regarding to the LSEA, which was the second most recommended technique and which is accompanied by the longest duration of action, the following prolonged motor blockage and potentially urinary retention that would require more intensive postoperative patient aftercare were

listed as negative facts. Smaller dogs were indicated as the most suitable for that approach, since the aftercare in those patients is much easier to ensure.
The survey in general turned out that no participant has recommended the nociceptive management without a locoregional anesthesia technique and particularly a combination of those is preferred (PNBs or LSEA combined with a peri-incisional infiltration). Interestingly, diplomates have mentioned that the preference between an EA and PNBs was associated with the time from board-certification and the employment sector. Furthermore, the decision making was influenced by the time pressure, surgeon preference and the patient's body size [48].

In relation to the chondrotoxic effects caused by local anesthetics, an in-vivo study performed by Ravnihar et al. has published that neither intact nor osteoarthritic diseased human stifle joint chondrocytes were negatively affected by a single intra-articular injection of 2 % Lidocaine. These findings support the hypothesis that cartilage damage originated by local anesthetic solutions is highly agent-, concentration- and exposure time-depended [49]. Further studies dealing with the long-term impact of various Lidocaine concentrations to the joint cartilage would be helpful for better estimation of this effect.

6 SUMMARY

The data evaluation shows well that the microarthrotomy and the tibial osteotomy were the surgical actions that have generated the strongest nociceptive signals. According to the four study protocols, no huge differences were detected within the first two study protocols which were exclusively based on systemically given drugs. The additional administration of a Fentanyl-Ketamine CRI has not revealed as being significantly advantageous. Pre-emptive Fentanyl boluses which were given prior to the surgical manipulations could control acute nociceptive stimulation to a certain extent and for a limited duration of time only. Disadvantageous was the occurrence of bradycardia as response to such boluses, which has occurred at individual variable threshold dosages.

The amplification of the ordinary analgesic protocol by a sole local femoral nerve anesthesia via Lidocaine in the majority of the dogs from study group 3 was not sufficient enough to prevent nociceptive signal transport during surgery of the hindlimb. This protocol was characterized by the worst antinociceptive efficacy, which means in particular that those dogs had the most severe parametric elevations in relation to the surgical manipulations. Fentanyl boluses were needed to administer merely to a little less extent (mean dosage 1,7 µg/kg BW) compared to the first two groups (mean dosages of 1,9 and 2,4 µg/kg BW). In summary it was noticeable that the dogs of the first three study groups had prominent fluctuations in the HF as expression of intraoperative nociception throughout the entire surgery.

The combination of the intra-articular stifle anesthesia via Lidocaine and the local sciatic nerve as well as the local femoral nerve anesthesia via a Lidocaine-Bupivacaine mixture as add-ons to the ordinary analgesic protocol finally turned out as being successful. Therefore, much less individuals responded with cardiovascular parametric elevations to the surgical manipulations and the dogs which did had significantly less severe percentage elevations form baseline values. In particular, 71 % of the patients from study group 4 did not even required an intraoperative Fentanyl rescue bolus at all. In the other ones, a mean dosage of 1 µg/kg BW Fentanyl was sufficient enough to provide an adequate antinociceptive support. However, the quantity of proband dogs in this study group was less than the half as in the first three groups.

As a general final conclusion it can be said that the antinociceptive management in dogs, in which sensitization processes have already amplified the nociceptive sensitivity, was definitely more challenging.

7 BIBLIOGRAPHY

1. Spinella G, Arcamone G, Valentini S (2021) Cranial Cruciate Ligament Rupture in Dogs: Review on Biomechanics, Etiopathogenetic Factors and Rehabilitation. Vet Sci 8:186. https://doi.org/10.3390/vetsci8090186
2. Binversie EE, Walczak BE, Cone SG, Baker LA, Scerpella TA, Muir P (2022) Canine ACL rupture: a spontaneous large animal model of human ACL rupture. BMC Musculoskelet Disord 23:116. https://doi.org/10.1186/s12891-021-04986-z
3. Di Bella C, Pennasilico L, Botto R, Salvaggio A, Galosi M, Staffieri F, Piccionello AP (2023) Efficacy of dexmedetomidine as adjuvant to bupivacaine in femoral-sciatic nerve blocks in dogs undergoing tibial plateau levelling osteotomy (TPLO). Res Vet Sci 154:124–131. https://doi.org/10.1016/j.rvsc.2022.12.015
4. Kerr CL (2020) Pain management l: systemic analgesics. In: Duke-Novakovski T, de Vries M, Seymour C (eds) BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition. British Small Animal Veterinary Association, Quedgeley, Gloucester, pp 124–142
5. Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (2020) Injectable Anaesthetic Agents. In: Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (eds) Veterinary anaesthesia: principles to practice, 2nd ed. Wiley-Blackwell, Hoboken, NJ, pp 77–94
6. Kästner SBR (2020) Injectable anaesthetics. In: Duke-Novakovski T, de Vries M, Seymour C (eds) BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition. British Small Animal Veterinary Association, Quedgeley, Gloucester, pp 190–206
7. Mülling C, Budras K-D (2012) Beckengliedmaße. In: Budras K-D, Mülling C, Pfarrer C, Reese S, Kölle S (eds) Atlas der Anatomie des Hundes, 9. Auflage. Schlütersche Verlagsgesellschaft mbH & Co. KG, Hannover, pp 136–157
8. Palmer RH (2005) Diagnosing cranial cruciate ligament pathology. https://www.dvm360.com/view/diagnosing-cranial-cruciate-ligament-pathology. Accessed 10 Apr 2023
9. Slocum B, Devine T (1983) Cranial tibial thrust: a primary force in the canine stifle. J Am Vet Med Assoc 183:456–459
10. Seo BS, Jeong IS, Piao Z, Kim M, Kim S, Rahman MdM, Kim NS (2020) Measurement of the tibial plateau angle of normal small-breed dogs and the application of the tibial plateau angle in cranial cruciate ligament rupture. J Adv Vet Anim Res 7:220–228. https://doi.org/10.5455/javar.2020.g413
11. Evans H, de Lahunta A (2009) Guide to the dissection of the dog, 7th ed. Saunders, St. Louis, Missouri
12. Salomon F-V (2015) Nervensystem, Systema nervosum. In: Gille U, Geyer H, Salomon F-V (eds) Anatomie für die Tiermedizin, 3. Auflage. Enke Verlag, Stuttgart, pp 477–628
13. Rooster H, Bruin T, van Bree P (2006) Morphologic and functional features of the canine cruciate ligaments. Veterinary Surgery 35:769-780 https://doi.org/10.1111/j.1532-950X.2006.00221.x

14. Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (2020) Local Anaesthetic Techniques for the Limbs: Small Animals. In: Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (eds) Veterinary anaesthesia: principles to practice, 2nd ed. Wiley-Blackwell, Hoboken, NJ, pp 215–236
15. O'Connor BL, Woodbury P (1981) The primary articular nerves to the dog knee. J Anat 134:563–572
16. Niebauer GW, Restucci B (2023) Etiopathogenesis of Canine Cruciate Ligament Disease: A Scoping Review. Animals 13:187. https://doi.org/10.3390/ani13020187
17. Hayashi K, Schulz KS (2019) Diseases of the Joints. In: Welch Fossum, Theresa T, Cho J, Dewey CW, Hayashi K, Huntingford JL, MacPhail CM, Quandt JE, Radlinsky MG, Schulz KS, Willard MD, Yu-Speight A (eds) SMALL ANIMAL SURGERY, 5th ed. Elsevier, Philadelphia, pp 1134–1279
18. Pelletier JP, Faure MP, DiBattista JA, Wilhelm S, Visco D, Martel-Pelletier J (1993) Coordinate synthesis of stromelysin, interleukin-1, and oncogene proteins in experimental osteoarthritis. An immunohistochemical study. Am J Pathol 142:95–105
19. de Bruin T, de Rooster H, van Bree H, Cox E (2007) Evaluation of anticollagen type I antibody titers in synovial fluid of both stifle joints and the left shoulder joint of dogs with unilateral cranial cruciate disease. Am J Vet Res 68:283–289. https://doi.org/10.2460/ajvr.68.3.283
20. Imholt KM, Möller S, Fehr M, Meyer-Lindenberg A (2011) [Lameness and osteoarthritis development following Tibial Plateau Leveling Osteotomy (TPLO) and potential prognostic predictors. A long-term retrospective study]. Tierarztl Prax Ausg K Kleintiere/Heimtiere 39:323–335
21. Nanda A, Hans EC (2019) Tibial Plateau Leveling Osteotomy for Cranial Cruciate Ligament Rupture in Canines: Patient Selection and Reported Outcomes. Vet Med Auckl NZ 10:249–255. https://doi.org/10.2147/VMRR.S204321
22. Kohn B, Reif U, Meyer-Lindenberg A, Wagner F (2018) Erkrankungen des Bewegungsapparates. In: Kohn B, Schwarz G (eds) Praktikum der Hundeklinik, 12. Auflage. Enke Verlage, Stuttgart, pp 1108–1189
23. Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (2020) Pain. In: Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (eds) Veterinary anaesthesia: principles to practice, 2nd ed. Wiley-Blackwell, Hoboken, NJ, pp 19–54
24. Klinck MP, Troncy E (2020) The physiology and pathophysiology of pain. In: Duke-Novakovski T, de Vries M, Seymour C (eds) BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition. British Small Animal Veterinary Association, Quedgeley, Gloucester, pp 97–112
25. Quandt J, Dewey CW (2019) Pain Management and Acupuncture. In: Welch Fossum, Theresa T, Cho J, Dewey CW, Hayashi K, Huntingford JL, MacPhail CM, Quandt JE, Radlinsky MG, Schulz KS, Willard MD, Yu-Speight A (eds) SMALL ANIMAL SURGERY, 5th ed. Elsevier, Philadelphia, pp 140–157
26. Moore SA (2016) Managing Neuropathic Pain in Dogs. Front Vet Sci 3:12. https://doi.org/10.3389/fvets.2016.00012
27. Hernandez-Avalos I, Mota-Rojas D, Mora-Medina P, Martínez-Burnes J, Casas Alvarado A, Verduzco-Mendoza A, Lezama-García K, Olmos-Hernandez A (2019) Review of different methods used for clinical recognition and assessment of pain in dogs and cats. Int J Vet Sci Med 7:43–54. https://doi.org/10.1080/23144599.2019.1680044

28. Lindley S (2020) Pain management lll: chronic pain. In: Duke-Novakovski T, de Vries M, Seymour C (eds) BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition. British Small Animal Veterinary Association, Quedgeley, Gloucester, pp 159–169
29. Grubb T, Lobprise H (2020) Local and regional anaesthesia in dogs and cats: Overview of concepts and drugs (Part 1). Vet Med Sci 6:209–217. https://doi.org/10.1002/vms3.219
30. Ossipov MH, Morimura K, Porreca F (2014) Descending pain modulation and chronification of pain. Curr Opin Support Palliat Care 8:143–151. https://doi.org/10.1097/SPC.0000000000000055
31. von Bernhardi R, Bernhardi LE, Eugenín J (2017) What Is Neural Plasticity? Adv Exp Med Biol 1015:1–15. https://doi.org/10.1007/978-3-319-62817-2_1
32. Pozzi A, Muir WW, Traverso F (2006) Prevention of central sensitization and pain by N-methyl-D-aspartate receptor antagonists. J Am Vet Med Assoc 228:53–60. https://doi.org/10.2460/javma.228.1.53
33. Johnston SA (2001) Overview of pain in the lame patient. Vet Clin North Am Small Anim Pract 31:39–53. https://doi.org/10.1016/s0195-5616(01)50037-6
34. Quandt J (2019) Principles of Anesthesia and Anesthetics. In: Welch Fossum, Theresa T, Cho J, Dewey CW, Hayashi K, Huntingford JL, MacPhail CM, Quandt JE, Radlinsky MG, Schulz KS, Willard MD, Yu-Speight A (eds) SMALL ANIMAL SURGERY, 5th ed. Elsevier, Philadelphia, pp 125–139
35. Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (2020) Concepts and Mechanisms of General Anaesthesia. In: Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (eds) Veterinary anaesthesia: principles to practice, 2nd ed. Wiley-Blackwell, Hoboken, NJ, pp 1–6
36. Grape S, Tramèr MR (2007) Do we need preemptive analgesia for the treatment of postoperative pain? Best Pract Res Clin Anaesthesiol 21:51–63. https://doi.org/10.1016/j.bpa.2006.11.004
37. Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (2020) Sedation and Premedication: Small Animals. In: Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (eds) Veterinary anaesthesia: principles to practice, 2nd ed. Wiley-Blackwell, Hoboken, NJ, pp 55–76
38. Murrell JC (2020) Pre-anaesthetic medication and sedation. In: Duke-Novakovski T, de Vries M, Seymour C (eds) BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition. British Small Animal Veterinary Association, Quedgeley, Gloucester, pp 170–189
39. Pang DSJ (2020) Inhalant anaesthetic agents. In: Duke-Novakovski T, de Vries M, Seymour C (eds) BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition. British Small Animal Veterinary Association, Quedgeley, Gloucester, pp 207–213
40. Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (2020) Local Anaesthetics. In: Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (eds) Veterinary anaesthesia: principles to practice, 2nd ed. Wiley-Blackwell, Hoboken, NJ, pp 191–204
41. Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (2020) Inhalation Anaesthetic Agents. In: Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (eds) Veterinary anaesthesia: principles to practice, 2nd ed. Wiley-Blackwell, Hoboken, NJ, pp 117–138

42. Duke-Novakovski T (2020) Pain management ll: local and regional anaesthetic techniques. In: Duke-Novakovski T, de Vries M, Seymour C (eds) BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition. British Small Animal Veterinary Association, Quedgeley, Gloucester, pp 143–158
43. Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (2020) Anaesthetic Breathing Systems and Airway Devices. In: Dugdale AHA, Beaumont G, Bradbrook C, Gurney M (eds) Veterinary anaesthesia: principles to practice, 2nd ed. Wiley-Blackwell, Hoboken, NJ, pp 139–166
44. Hughes L (2020) Breathing systems and ancillary equipment. In: Duke-Novakovski T, de Vries M, Seymour C (eds) BSAVA Manual of Canine and Feline Anaesthesia and Analgesia, third edition. British Small Animal Veterinary Association, Quedgeley, Gloucester, pp 45–64
45. Caniglia AM, Driessen B, Puerto DA, Bretz B, Boston RC, Larenza MP (2012) Intraoperative antinociception and postoperative analgesia following epidural anesthesia versus femoral and sciatic nerve blockade in dogs undergoing stifle joint surgery. J Am Vet Med Assoc 241:1605–1612. https://doi.org/10.2460/javma.241.12.1605
46. Sarotti D, Ala U, Franci P (2022) Epidural anesthesia in dogs undergoing hindlimb orthopedic surgery: effects of two injection sites. J Vet Med Sci 84:457–464. https://doi.org/10.1292/jvms.21-0289
47. Kalamaras AB, Aarnes TK, Moore SA, Jones SC, Pereira CR, Peng J, Kieves NR (2021) Effects of perioperative saphenous and sciatic nerve blocks, lumbosacral epidural or morphine–lidocaine–ketamine infusion on postoperative pain and sedation in dogs undergoing tibial plateau leveling osteotomy. Vet Anaesth Analg 48:415–421. https://doi.org/10.1016/j.vaa.2021.02.004
48. Parker LA, Bukoski AD, Zelaya-Nunez C, Dodam JR, Varner KM, Torres BT (2023) Pelvic limb anesthesia and analgesia in dogs undergoing tibial plateau leveling osteotomy (TPLO): A survey of board-certified anesthesiologists. Vet Surg 52:521–530. https://doi.org/10.1111/vsu.13947
49. Ravnihar K, Marš T, Pirkmajer S, Alibegović A, Koželj G, Stožer A, Drobnič M (2021) The Influence of a Single Intra-Articular Lidocaine Injection on the Viability of Articular Cartilage in the Knee. Cartilage 13:456S-463S. https://doi.org/10.1177/1947603520904759

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I hereby confirm that I am familiar with the content of the thesis entitled

A comparative study of different pain management protocols in the perioperative period on cranial cruciate ligament ruptured dogs which undergo TPLO surgery

written by Marlena Schultze, which I deem suitable for submission and defence.

Date: Budapest, 2023...11...08...

Dr. Csilla Simon

.....

Supervisor name and signature

Department of Small Animal Surgery

Thesis progress report for veterinary students

Name of student: Marlena Schultze

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Name and title of the supervisor: Dr. Csilla Simon

Department: Department of Small Animal Surgery

Thesis title: A comparative study of different pain management protocols in the perioperative period on cranial cruciate ligament ruptured dogs which undergo TPLO surgery

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2022.	09.	29.	Thesis theme and structural consultation	
2.	2022.	10.	13.	Introduction of the clinical life	
3.	2022.	11.	10.	Patient monitoring and anaesthesia	
4.	2022.	11.	24.	Patient monitoring and anaesthesia	
5.	2022.	12.	8.	Patient monitoring and anaesthesia	

Grade achieved at the end of the first semester: 5

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Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023.	03.	23.	New protocols Patient monitoring and anaesthesia	
2.	2023.	04.	06.	Patient monitoring and anaesthesia, collection of datas	
3.	2023.	05.	11.	Patient monitoring and anaesthesia, collection of datas	
4.	2023.	06.	8.	Patient monitoring and anaesthesia, collection of datas	
5.	2023.	06.	22.	Literature analysis, Patient monitoring and anaesthesia, collection of datas	

Grade achieved at the end of the second semester: 5

Dr. Simon Csilla 1009

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

.....

Signature of the supervisor

Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis in: 2023.11.06.