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**The pain relieving effect of the gold bead implantation in the canine
hip dysplasia in comparison with other studies and the palliative
effect of non-steroidal-anti-inflammatory drugs**

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1. Abbreviations

Approx = approximately

CI = confidence interval

CHD = canine hip dysplasia

COA = canine osteoarthritis

Cox = cyclo-oxygenase

e.g. = exempli gratia / for example

et al. = et alii (and others)

etc. = et cetera (and so on)

FHO = femoral head ostectomy

G = gauge (size of needle)

GI = gold bead implantation / acupuncture

Hz = Hertz

I- κ B = nuclear factor kappa-light-chain-enhancer of activated B cells inhibitor

IKK = nuclear factor kappa-light-chain-enhancer of activated B cells inhibitor kinase

IL = Interleukin

ITO = intertrochanteric varisation osteotomy

M = musculus

NF- κ B = nuclear factor kappa-light-chain-enhancer of activated B cells

NKA = neurokinin A

NPY = neuropeptide Y

P = probability of α -error

PIN = pectineus- and iliopsoas myotomy with ventral neurectomy

SP = substance P

TCM = traditional Chinese medicine

TNF- α = Tumor-necrotic-factor- α

TPO = triple pelvic osteotomy

% = percent

2. Abstract

Canine hip dysplasia (CHD) is a common inherited degenerative disease of the hip joint mostly affecting large sized dogs. The degree of pain due to CHD is highly individual with some dogs showing no signs of pain while others show severe locomotive disorders with a high degree of pain. In the past the only possible treatments consisted of surgical interventions or life-long pharmacological therapy with drugs usually from the family of the non-steroidal anti-inflammatory drugs (NSAIDs). The gold bead implantation (GI) is a relative new alternative palliative treatment possibility for CHD. The aim of a GI is to reduce the amount of pain caused by CHD. While the acupuncture in the human medicine has a long tradition, acupuncture in veterinary medicine, and therefore also the GI, has become more famous in the last decades. Acupuncture elicits the pain relieving potential by releasing neurotransmitters acting as agonists on opioid receptors, increasing the threshold for pain, and by modulation of the activity of cytokines. The way of action of the gold is via the inhibition of the I- κ B kinase and subsequent binding of NF- κ B to the DNA in the nucleus. Through the non-activation of this protein the production of pro-inflammatory cytokines as TNF- α , IL-1- β , IL-6 etc. is inhibited. Without the stimulation of the cyclo-oxygenase-2 (Cox-2) by these cytokines no prostaglandins, responsible for the inflammatory process, can be produced. The NSAIDs inhibit the stimulation of Cox enzymes directly. New developed highly selective NSAIDs have the Cox-2 as main target and are able to spare the Cox-1 responsible for different physiological functions within the body. In the past the effect of the GI treatment was compared in several double-blinded studies which came to quite different results. Therefore, in the scope of this thesis the effectiveness of the GI therapy should be compared with the effectiveness of two NSAIDs (carprofen and firocoxib). The trial with the GI therapy was an open study over two years and the trials with the NSAIDs were double-blinded trials. The results showed that the GI had a significant effect after one week which was increasing significantly over six months and staying then more or less constant. In comparison with the results of the NSAIDs it was shown that the GI therapy had a greater effect than carprofen. But it was equal with the effectiveness of firocoxib. However, the results also showed that in the trial with NSAIDs several dogs were suffering from the typical adverse effects caused by NSAIDs. Even in the group treated with firocoxib, a relative safe drug, some dogs suffered from stomach ulcers, whereas no dogs of the GI group had any adverse effect.

3. Introduction

The topic of this thesis is the pain relieving effect of the gold bead implantation in the canine hip dysplasia in comparison with other studies and the palliative effect of non-steroidal-anti-inflammatory drugs.

The CHD is a chronic non-curable degenerative disease (Janutta et al., 2006; Hielm-Björkmann, 2007; Ginja et al. 2009). Previous to the GI the only therapy for CHD consisted either of rigorous surgical interventions or the administration of NSAIDs. Before the detection of new isoforms of Cox-enzymes and the design of highly selective inhibitors only non-selective Cox-inhibitors which easily cause strong adverse effects were available. Even nowadays the potential side effects of NSAIDs from the newest generation can be very problematic in the life-long therapy of the CHD. The GI could be therefore an alternative or addition to these two therapies. However, the gold bead implantation is a relative new alternative palliative treatment and is still considered controversial among veterinarians. In the past only a few studies about the effectiveness of the GI were published and no study was published in which it was compared to other treatments. The published studies in which a placebo group was used came to quite different results. Some investigations could not observe any significant difference between a treated and a placebo group (Hielm-Bjorkman et al., 2001). Other studies however observed a highly significant difference between a placebo and a GI treated group (Jaeger et al., 2007)

In the scope of this thesis two studies dealing with the effect of the GI compared to a placebo group should be evaluated. One study came to a non significant difference between a placebo and GI treated group. The second study recognized a significant difference between a placebo and GI group. A third study will have the target to get own results which could be then compared to the mentioned two studies and with studies concerning the pain relieving effect of NSAIDs.

The expectation of the third study is that the gold bead implantation shows an effect after one week. The pain relieving effect will then significantly increase during the following six month and till the end of a 24 month period it will slightly decline due to the fact that it is just a palliative therapy and not a curative therapy.

4. Hip dysplasia

The canine hip dysplasia is a common inherited non-congenital disease of dogs (Janutta et al., 2006; Hielm-Björkmann, 2007; Ginja et al., 2009). In CHD the hip joint shows gradual morphological changes and incongruence of the different structures (Fries and Remedios, 1995; Janutta et al. 2006) and due to these changes secondary joint diseases like chronic osteoarthritis will develop. At the time of birth the hip looks normal and no obvious changes in the morphology of the joint can be detected (Fries and Remedios, 1995). CHD develops during the fast growing period of the young dog (Janutta et al. 2006). In mature animals the joint then shows several morphological changes in its structures. The cartilage will be degenerated and the capsule will be thickened. The bones of the joint will undergo a certain remodeling too. The neck of the femur will get thicker and the acetabulum will show also a proliferation at the dorsal part. The accompanying muscle will be more or less atrophic due to the lack of activity (Fries and Remedios, 1995; Hielm-Björkmann, 2007). However the clinical sign of the CHD can be highly individual. Some dogs will show a high grade of lameness with less structural changes of the joint while others will show no or only a slight lameness with heavy structural changes of the joint structures (Hielm-Björkmann, 2007; Ginja et al., 2009). Sometimes the animal will show only a laxity of the joint during walk (Fries and Remedios, 1995; Janutta et al., 2006). To classify the degree of the CHD three different grading systems exists in the USA, the UK and in the continental Europe (Ginja et al., 2009).

Figure 1 shows a healthy hip joint and Figure 2 a dysplastic hip joint. If there is no radiographic signs of a CHD the centre of the femoral head should be located medially from the cranial border of the acetabulum and its dorsal structures have to shadow more than 50% of the head. The joint space should be even and the two edges of the bones (femur and acetabulum) should be congruent to each other. Furthermore the bones should not show any abnormal progressive or regressive changes in its structure and no osteophytes should be seen (Fries and Remedios, 1995).



Figure 1 (healthy hip)
(Tierärztliche Gemeinschaftspraxis, 2015)



Figure 2 (hip with CHD)
(Tierärztliche Gemeinschaftspraxis, 2015)

5. Possible therapies of a CHD

In veterinary medicine different approaches exist to treat CHD. They can be classified as surgical, pharmacological or alternative treatment. The surgical interventions can be subdivided into curative non-amputating, curative amputating and non-curative. To the first subgroup belongs the triple pelvic osteotomy (TPO). Another possible curative surgical intervention in young animals is the intertrochanteric varisation osteotomy (ITO). The extension of the femoral neck is also possible with the aim through elongation of the femur to place back the head of it into the acetabulum. The fourth curative non-amputating surgery is the acetabulum roof reconstruction. The requirements for these four surgeries are that CHD has to be detected in the beginning of the process and the surfaces of the joint

cartilage have to be intact. While the TPO, ITO and the extension of the femoral neck have the best results in still growing dogs the reconstruction of the acetabulum needs only intact joint surfaces. The class of curative amputating methods consists of two potential surgeries. The first one is the femoral head ostectomy (FHO) with the removal of the complete head. The second surgery is the total endoprosthesis of the hip joint. Both can be performed in mature dogs with advanced CHD and already degenerated joint surface. The palliative surgical intervention consists of the pectineus-myotomy, pectineus- and iliopsoas myotomy with ventral neurectomy (PIN) and the dorsal denervation of the joint capsule (Fries and Remedios, 1995; Müller, 2004). The pharmacological therapy achieves the palliative aim by reducing the degree of pain and inflammation. The most common drugs belong to the NSAIDs. Sometimes they are combined with glycocorticoids (Brooks and R. O Day, 2000). The way of action of NSAIDs as well as their adverse effects will be discussed later in this thesis. The third class is the alternative therapy. This class is relative new and only few studies are available addressing the effectiveness of them. To this class belong the GI, normal acupuncture, miscellaneous naturopathies and homeopathy (Hielm-Björkmann, 2007).

6. Acupuncture in the medicine

6.1 History, concepts and types

Traditionally acupuncture derives from the TCM and has been practiced for more than 2000 years (Langevin et al., 2001). The use of acupuncture in the medicine was first mentioned in the 2nd century BC in ancient Chinese texts. During the 17th and 19th century the knowledge of the effect of acupuncture spread from China to Europe but only few experiments of the therapeutic use were done. In the 20th century the therapeutical use of acupuncture was expanding in the USA and Europe (Helms, 1998). In the 1950s investigation indicated a potential effect of acupuncture to relieve pain after surgical procedures (Han, 2004). Although according to ancient Chinese traditions acupuncture was used to treat various diseases, in the Western countries it was mainly the therapeutic use against (chronic) pain that was established (Bucinskaite et al., 1994). Further investigations showed an analgesic effect through the release of endogenous opioid peptides and biogenic amines causing a change in processing and transmitting of noxious information in the

central nervous system. Normally during the acupuncture fine needles are inserted into the body. According to the pattern of the insertions three different concepts can be identified. The classical concept relating from ancient Chinese texts describe an own anatomy of the body consisting of energy channels called meridians (Helms, 1998; Langevin et al., 2001). These meridians are named according organs and build a network from four different types of channels (tendinomuscular, principal, distinct and the curious meridians). The diagnosis is set according to subtle spheres of influence and the needles are inserted into the body along these meridians to restore the physiological function and balance. The modern concept exists since the 1970s and involves two systems (endorphin-dependent and monoamine-dependent). Through combination of these two concepts a hybrid form can be named. The hybrid form is seen as an activation of multiple systems simultaneously in the body. The four systems are the nervous system, the blood circulation, the lymphatic system and the electromagnetic bio-information system. Currently three types are distributed in the Western countries. In the USA the traditional acupuncture and in Europe the five elements acupuncture is common. Beside these two types the somatotopic acupuncture, consisting of the auricular, hand and scalp acupuncture, could develop. During acupuncture the needles are left in place for approx. 5 to 30 minutes (Helms, 1998). In the past a supporting additional simulation was the grasp of the needle. This was then further refined to the electro-acupuncture (Helms, 1998; Langevin et al., 2001). Another supporting stimulation is the moxibustion (heating of the needle). The Interval between two sessions of acupuncture can differ from 1 week to 2 months sometimes even up to 2 years (Helms, 1998).

6.2 History of veterinary acupuncture

In many articles and books it is mentioned that veterinary acupuncture has a long tradition in the Chinese culture. However, often it is unclear if the ancient texts are referring to acupuncture as we know it. The problem with the old Chinese resources is that in these texts the word *zhen* is used which means “needling”. In the past the expression needle was used not only for thin metal needles but also for longer blades, lancets etc. Therefore the word “needling” can be translated with acupuncture but also with bleeding, opening abscesses, cauterization etc. The reason of the mistranslation is that mostly the authors of these texts are different persons as the potential acupuncturist. Many of the ancient texts about an acupuncturist were written long after his death. Furthermore these texts are very old and parts got lost over the centuries and were refilled from the new author. In addition the ancient literature mentions only “points” which does not mean that these are really acupuncture points similar in the human acupuncture medicine. For a “point” to be within the context of acupuncture it has to be together with the words *qi* and *mai* “vessels” where the *qi* is flowing. Sometimes the mentioned points are just areas to open a blood vessel for bleeding or other treatments (Imrie et al., 2001). In summary it can be said, that veterinary acupuncture is not an ancient medicine. The ancient veterinary discipline can be more quoted as naturopathy. The use of acupuncture in the veterinary medicine was more likely developed in the modern time. During the last 50 years the effect of the acupuncture in veterinary medicine has been the target of several studies and knowledge about the mechanism of acupuncture has received a more scientific basis. In the USA veterinarian started to use the gold bead implantation to treat CHD (Danscher, 2006).

6.3 Effect of the medical acupuncture

The effect of the acupuncture is based on the release of different mediators acting as agonists at the μ - and κ -opioid receptors (Han, 2004) including endorphins and monoamines (Helms, 1998) as well as several neurotransmitters. The monoamines were first investigated and the neurotransmitter serotonin was identified as playing a role in the mediation of the analgesic effect of acupuncture (Han, 2004). Further studies detected also an increase in the neurotransmitter SP, NPY and NKA in the hippocampus and the occipital cortex after electro-acupuncture causing a higher threshold of pain (Bucinskaite et al. 1994). Two types of electro acupuncture are used nowadays. The first type uses a low frequency of 2 Hz and the second type a frequency of 100 Hz (Helms, 1998). The 2 Hz frequency is able to induce a release of enkephalin, β -endorphin and endomorphin. A frequency of 100 Hz is responsible for the release of dynorphin. From these four agonists the dynorphin is acting on the κ -receptors and endorphin on the μ -receptors. Enkephalin and β -endorphin are mixed agonist acting on μ - and δ -opioid receptors. A therapy changing the frequency between 2 and 100 Hz is possible to stimulate the release of all four agonists to achieve a strong analgesic effect (Han, 2004). Other studies detected that acupuncture modulates the action of cytokines and growth factors too. As a result of this effect acupuncture is also able to modulate indirectly the effect of the Cox-2 receptors (Langevin et al., 2001; Pollmeier et al., 2006). Furthermore, it was discovered that acupuncture is able to cause a change in the connective tissue environment through the modulation of the cytoskeleton of the fibroblasts and the extracellular matrix. This change may play a role in the effect of acupuncture in places more farther away from the insertion of the needles. However more detailed studies should investigate this potential in the future (Langevin et al., 2001).

7. Gold in the medicine

7.1 Liberation of gold and its possible effect

The exact mode of action of gold in the different therapies is still not known. However in recent studies it was shown that phagocytic polynucleated cells surrounding a solid gold plate were able to liberate gold from its metallic form extracellularly in vitro through oxidative chemical reactions. This activity can be enhanced through the activation of macrophages in inflamed tissues like in the CHD (Yang et al., 1995; Jeon et al., 2000; Larsen et al., 2007). Other studies identified the connective tissue as the location of the liberation process in the animal. After the liberation subsequent charged gold ions (aurocyanide) were formed. It was detected that the longer the gold was in the tissue the more charged gold ions were found in different cells further away from its insertion. After a period of two weeks gold was found at the side of the lesions and also at the border between inflamed and healthy tissue (Danscher, 2006; Larsen et al., 2008). Furthermore, it was detected that gold can influence the immune reaction in the chronic inflamed tissue of an arthritic joint. The level of pro inflammatory cytokines was reduced in the tissue through the modulation of the function of phagocytising cells (Yanni et al., 1994; Yang et al., 1995; Jeon et al., 2000; Danscher, 2006; Larsen et al., 2007; Larsen et al., 2008). The modulation is elicited by the suppression of the NF- κ B binding activity to the DNA via the inhibition of the IKK (Jeon et al., 2000; Danscher, 2006). The protein NF- κ B is present in a latent form in the cytoplasm of different cells. Normally it is sequestered by the interaction of I- κ B and NF- κ B proteins. The I- κ protein is phosphorylated by the IKK and will subsequent degrade from the NF- κ B. Through the degradation of I- κ B the NF- κ B will be liberated and is then able to translocate into the nucleus and able to bind to the DNA. Through the binding to the DNA genes are expressed which are responsible for the production of different pro-inflammatory cytokines (Yanni et al., 1994; Yang et al., 1995; Jeon et al., 2000; Larsen et al., 2007). The inhibition through charged gold ions of the IKK prevents the liberation of NF- κ B and consequently the binding of it to the DNA. Hence the non-activation of specific genes in the DNA hinders the production of the different cytokines (TNF- α , IL-1- β , IL-6, macrophage-inflammatory-protein and chemokines) (Tegeger et al., 2001; Tegeger et al., 2004). In other studies it was detected that the number of activated macrophages was also reduced in synovial membranes like in arthritic joints. In an animal trial with rats an implantation close to a joint was able to provoke a strong reduction of the inflammatory process and to relieve the animal from pain. For obtaining a

therapeutic effect it is suspected that a relative small dosage of gold is sufficient. In the mentioned study with rats it was demonstrated that the material used for therapy should have a density of minimum 4.5 g/cm^3 which gold is fulfilling with 19.32 g/cm^3 . However it was investigated that a higher amount of gold has a greater effect of the surrounding tissue (Yanni et al., 1994; Danscher, 2006; Larsen et al., 2007).

7.2 Use of gold in the human medicine

Since 1930 gold salts like sodium aurothiomalate are used against rheumatic and psoriatic arthritis in the human medicine. In ancient times gold was also used in the therapy against tuberculosis and other diseases. For the therapy of rheumatic arthritis the gold salts are either injected locally close to the affected joint or, since 1979, oral administered. Because of the strong nephro-toxicity as severe adverse effect the dosage has to be carefully calculated (Freyberg et al., 1941; Danscher, 2002; Larsen et al., 2007; Larsen et al., 2008; Sanella et al., 2008). Recent studies detected also a possible use of gold in the therapy against malaria. It was shown that gold has a strong inhibitory effect on thioredoxin reductase. This enzyme was believed to be a possible target against several diseases which is why recent trials tried to detect the possible re-use of gold in different diseases. Trials noted that gold can potently inhibit the growth of Plasmodium species, the causative of malaria in vitro. The cyto-toxicity of gold, responsible for the potential damage of the kidney, is used in the therapy of cancer too (Danscher, 2002; Sanella et al., 2008). Other trials with rats showed that gold ions were also able to reduce the apoptosis of neurons in injured brain tissue, to decrease the inflammation and to enhance the regenerative potential of the tissue via increasing the mitotic activity of stem cells. The amount of gold could be reduced in that trial to a minimal amount to a lower dosage causing nephro-toxicity. Further studies are going on to investigate the possible use of gold in ameliorating neuroinflammation (Larsen et al., 2008). However the use of gold in endo-implants in the human medicine declines and is being replaced more and more by the metal titanium.

7.3 Adverse effects of gold

Since 1930 gold salts were widely used in the therapy of the rheumatic arthritis as mentioned before. However no scientific researches about the effect, metabolism or adverse effects were available at that time. Empiric experiences showed that gold salts could cause allergic reactions and sometimes even kidney failure. A study from Freyberg et al. (1941) could detect that the type and degree of adverse effects in the gold therapy were dose-dependent. Patients treated with a high weekly dosage (50 mg) of gold showed more or less severe adverse reactions like generalized exfoliative dermatitis, nephritis, stomatitis etc. Other adverse effects were not dose dependent, and occurred in patients receiving a dosage of 50 mg or 25 mg. The patients were temporally suffering from headache, tightness in the throat and temporal purpuric dermatitis. More recent studies could then detect that the anti-inflammatory effect of gold was still present in a much lower dosage where adverse effect were not likely to occur (Larsen et al., 2008). Articles concerning adverse effects cause by gold liberated from implants were not available.

8. Gold bead implantation

8.1 Aim of the gold bead implantation

Due to the fact that most of the patients visiting the clinic are mature and already show signs of a secondary chronic COA the aim of the treatment is of a palliative nature. It means that in most of the cases it is too late to prevent the formation of the secondary degenerative changes in the morphology of the joint like it is done in the human medicine (Ginja et al., 2009). The treatment of the implantation of gold beads is aimed to reduce the pain and to improve the function of the hip joint (Jaeger et al., 2012).

8.2 Methods to perform the gold bead implantation

In general the visit of the owner can be grouped according two reasons. In the first group the owner visits the clinic for a general examination or to make a radiographic picture of the hip due to the bylaws of a dog club. In this group it is possible to detect a CHD before the onset of any clinical signs and a prophylactic GI can be recommended to the owner. The second group visits the clinic after the onset or a worsening of clinical signs is

detected at home. The typical signs observed by the owner at home are mostly certain stiffness, difficulty in rising, climbing stairs, jumping over obstacles or reluctance for activity (Ginja et al., 2009). The veterinarian then examines the animal in the clinic to locate the origin of the lameness and to grade its severity. The examination procedure involves the anamnesis, general and detailed examination. The detailed examination should include the gait analysis, palpation of the hip joint and probably of several trigger points and radiography.

8.2.1 Anamnesis

A detailed anamnesis is very important for the successful therapy and is performed before the clinical and detailed examination. During this part of the examination the veterinarian tries to get as much information as possible from the owner about the changes in the behavior or signs of pain detected at home as well as earlier treatments concerning the lameness of the dog.

8.2.2 General clinical examination

This part of the examination can also be done another day in the near future in order to reduce the stress for the patient. The goal of the general clinical examination is to determine the general status of the animal and the possible risk of the narcosis during the implantation. Additional to the clinical examination the veterinarian can also take a blood sample to check the organ profile, which gives important data to calculate the risk of a narcosis especially in older patients (Kasper, 2005a).

8.2.3 Detailed examination

The detection of CHD can be very difficult. As mentioned above the grade of lameness does not always conform to the structural changes of the joint and the clinical signs of the CHD can be highly individual. Particularly the early diagnosis can be very difficult. When the dog is a young puppy the hip joints have no obvious morphological changes and often the dog shows no signs of pain yet. Due to this fact a prophylactic treatment is rarely done on the basis of the clinical signs. To detect a CHD before the onset of clinical signs a radiographic picture of the hip at the age of 24 month is more reliable and therefore advisable (Fries and Remedios, 1995; Kasper, 2005a).

8.2.4 Adsppection

The visual examination is done first in rest and later in motion (gait analysis). The veterinarian should evaluate the relationship between the weight, size, shape, ratio of muscles and the age. In the next step the veterinarian evaluates the posture of the body and the bearing of the limbs. During this part of the examination they look for any signs of lameness or a relieving posture (Kasper, 2005a).

8.2.5 Analysis of the gait pattern

The analysis of the gait pattern is a special part of the inspection. This analysis gives information about the situation of the pain during motion (Kasper, 2005a). Several studies indicated that every person has an own scoring system of the severity of lameness which differs from other examiners. Therefore to achieve an accurate scoring all the lameness examination of one dog should be performed by the same veterinarian (Quinn et al., 2007). During the examination the veterinarian should evaluate the situation in slow, medium fast and fast walk as well as in slow, medium fast and fast trot. The observation of the dog is done from the side, the back and from the front. Most information is received in walk because the dog does not get any swing from the forward movement and has to stretch the joints completely (Kasper, 2005a). For research studies it is advisable to perform a force gait analysis to achieve good results. But in most of the cases the GI will be done in a private veterinarian clinic. For practical reasons it is enough to examine the gait outside

without a force plate (Quinn et al., 2007). The area outside should be approx. 20 – 25 m long and the ground flat, dry and not slippery (Kasper, 2005a). Table 1 shows the main types of lameness concerning hip joint dysplasia. The left side of the chart shows the findings during the gait analysis while the right side shows the different causatives for these findings. These findings are not only seen in dysplasia of the hip joint but also in other diseases causing lameness of the hind leg and are also mentioned briefly within the table 1.

Finding	Causative
Twist of the lumbo-sacral joint in walk	Primary hip problem; resulting in secondary twisting of the lumbo-sacral joint
One side of the stays up during walk	Blocking in the iliosacral joint; mostly secondary in hip dysplasia, pain originating from the stifle joint or the last lumbar vertebrae
One side of the hip stays down during walk	Hip problem; during lifting off the hind leg the hip joint is not stretched completely
Narrow knees and/or close to the ground in trot	Hip problems like COA due to CHD
Shortening of the length of steps	Forward movement is painful indicating problems with the iliosacral joint, hip joint or the M. quadriceps femoris
„Bunny hopping“	severe pain due to secondary osteoarthritis
Reduction of height of steps	COA due to CHD

Tabel 1 (findings in the lameness examination and causatives) (Kasper, 2005a; Hielm-Björkmann, 2007; Ginja et al., 2009)

To exclude any neurological problems of the back part the patient should perform special exercises like turns or walking down and up the edge of the pavement too (Kasper, 2005a; Hielm-Björkmann, 2007; Ginja et al., 2009).

8.2.6 Palpation

The palpation is performed after the gait analysis; otherwise the palpation would disturb the evaluation of the gait pattern by potentially provoking pain. The palpation is used to find the exact origin and to determine the intensity of pain. First the back should be palpated: the veterinarian presses their thumb or the index finger paramedian to the spinal processes with equal pressure on the left and right side at the same time. The fingers press gently at first, and then pressure is increased with rotating movements. The evaluation of the intensity of pain is based on how much pressure is needed to provoke a reaction from the patient. These reactions can be for example the smacking with the lips, a short arresting of the breathing, panniculus-reflex or defense reaction against the examiner (Kasper, 2005a). The types of palpation used for the hip joint can be divided into two groups according to the age of the dog. During the examination of the younger patients which have a laxity of the hip joint as main problem special tests are performed like the Ortolani-, Bardens- and Barlow-test. For the procedure of these tests it should be referred to the orthopedic literature. These tests are not performed in older patients as they are usually suffering already from secondary chronic osteoarthritis. In these dogs the veterinarian palpates the accompanying muscles of the hip joint and of the hind leg to detect any signs of atrophy due to inactivity and to detect potential regions causing pain in the hip area. Furthermore the range of movement of the hip joint is examined and evaluated (Ginja et al., 2009).

A special part of the palpation is to examine the trigger-points. These are special points in the musculature which always react if there is a painful reaction in a certain region in the body. These reactions are local indurations of the muscle which are sensitive to pressure (Melzack et al., 1976; Kasper, 2005a). However, the use of trigger points in diagnoses is questionable. On the one hand it has been proven that they react to pain in other regions. But it should also be considered that a stimulation of these points is able to cause a noxious sensation for several hours (Melzack et al., 1976). After the GI the result of the trigger points will change to negative 1 to 1.5 years after the gold implantation. According to this fact the trigger points cannot be examined in the aftercare anymore (Melzack et al., 1976; Kasper, 2005a). Related to hip pain two trigger-points could be used for diagnosis. The first one is the MA 31. The point is located on the cranial part of the thigh at the M. rectus femoris a little bit distal of the hip joint. To examine this point the examiner should stand

behind the animal and try to feel the knee fold. Moving the fingers proximal a groove between the M. tensor fasciae latae, M. vastus lateralis on the lateral side and the M. satorius on the medial side can be felt. In this groove he lays 2-3 fingers depending on the size of the dog. Under constant pressure the fingers pull the groove caudally. The pressure starts again first gently and increases with time. A negative result is when the dog is working against this pull and it is hardly manageable to bring the dog out of balance even with strong pressure. All other results have to be counted as positive. It is to take into account that this trigger point gives information about pain in the hip region in general and not only about the hip itself. This includes all organs in this region like the prostate and the urinary bladder as well. Especially in older male dogs a dysfunction of the prostate can result in a positive reaction of this trigger point. The second trigger point is the MA 32. This point is located at the M. rectus femoris like the MA 31 too. The point is a little bit more proximo-lateral of the knee where the muscle body of the M. vastus lateralis runs over to its tendon. This point gives information mainly about the stifle joint and to a lesser amount about the hip joint. Due to this fact this trigger point is not regularly examined (Kasper, 2005a).

8.2.7 Radiography

After the adpection and palpation the area of interest can be located. If the veterinarian locates the hip as the origin of pain the next step is to perform a typical stress-radiographic picture to detect a CHD. To perform an accurate radiographic examination the dog should be under general anesthesia to relax the muscles completely. The hind legs should be extended and parallel to each other and to the spin in a ventro-dorsal recumbence (Fries and Remedios, 1995). The person who holds the hind legs should rotate the leg inwardly. In the x-ray picture the patella should be in the centre of the condyles of the femoral bone and not rotated. A rotation of the hip is also to avoid. A comparison of the two sides of the ala coxae can help to estimate if the hip is rotated or not. In the case of prophylactic GI it is very important to look for the slightest changes. If there is a large gap between detection of the CHD and the GI procedure, two new radiographs should be performed just prior to the procedure. This ensures an accurate picture about the present state of the joint (Jaeger et al., 2012). One picture should show the hip in latero-lateral recumbence and the second picture in a 90° angle position in ventro-dorsal recumbence. (Kasper, 2005a)

8.2.8 Points to treat

The number of treated points varies in the different techniques of the GI. For simplicity only the four points used in the GI of the study in the scope of this thesis should be explained. Three of the points are classical acupuncture points and one is not an acupuncture point but rather a triggerpoint. The classical acupuncture points are GB 29, GB 30 and GB 31 and the non-acupuncture point is the GB 29.5. This name of this point arrives due to the fact of the localization between the point 29 and 30. In other studies the point was named BL 54 (Kasper, 2005a; Jaeger et al., 2012). A scheme can be seen in the drawing (figure 3).

GB 29: cranio-lateral to the acetabulum on the ala ossis ilii approx. 1 to 1.5 cm cranial from the highest point of the trochanter major.

GB 30: proximal to the trochanter major on the level of the imagined elongation of the femur axis.

GB 29.5: between GB 29 and 30.

GB 31: caudal to the trochanter major on the corpus ossis ischii.

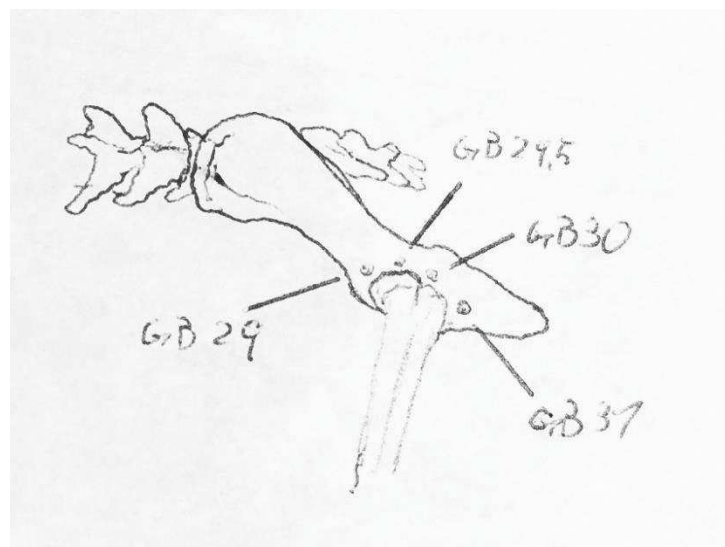


Figure 3: sketch of the hip and points to treat
(Nickel et al., 1954)

8.2.9 Material used in the gold implantation

To perform a GI procedure a gold wire of 24 karat and a length of approx. 2 mm is used. To open the skin a small scalpel for example of the size 15 is needed and for placing and handling of the small gold pieces a forceps, Adson-Brown or Splinter forceps is needed. To insert the gold close to the joint a hollow metal needle of a length of 4 to 10 cm and a size of 14 G as well as a mandrin which is filling the lumen of the needle should be used. The best mandrin is a Kirschner drill wire of a length of 15 to 20 cm. However every metallic stylet filling the lumen can be used. To close the incision wounds normal suture material would be enough. From the sanitary aspect swabs and surgical draping is also needed to avoid any kind of contamination and following infection. All materials used in the implantation of the gold beads should be sterilized and placed on a sterile instrument table (Kasper, 2005a; Jaeger et al., 2012).

8.3 Method of implantation

8.3.1 Pre-operative

During the implantation the animal lies in lateral recumbence to provide access to the lateral hip joint. To avoid uncontrolled movements of the animal general anesthesia has to be used. The operation field has to be shaved (in a square of 10 x 10 cm approx) and two times disinfected to be able to achieve aseptic conditions (Jaeger et al., 2012).

8.3.2 During the implantation

While the veterinarian implants the gold an assistant should hold the leg in a horizontal position. To localize the different implantation points the highest point of the trochanter major in the centre can be used as orientation. To open the skin a stab incision over the implantation point has to be performed. After the opening of the skin the veterinarian introduces a metal hollow needle perpendicular to the bone until he can feel the surface of the bone. The opening of the needle points away from the joint and after reaching the intended place the needle is turned so the opening is pointed now toward the joint. For every implantation point 1 to three gold pieces should be inserted according the degree of

pain. However, some studies mentioned that it is probably unimportant how many beads are implanted (Jaeger et al., 2012). In other studies it was shown that the number of gold beads for each treated point should be increased in cases of highly painful CHD (Kasper, 2005a). With the mandrin, for example a Kirschner wire, the gold pieces can be held in place while the needle is removed. Several studies emphasized that it is important to avoid the insertion of any gold beads within the joint but rather close to the capsule of the joint (Jaeger et al., 2012). To prevent the insertion of the gold beads into the joint the veterinarian has to check for any synovial leakage out of the cone of the needle. In the case of leakage the placement of the tip of the needle has to be corrected. Special care has to be taken for the point M 30. The position of this point is close to the sciatic nerve and a penetration of it has to be avoided (Jaeger et al., 2012).

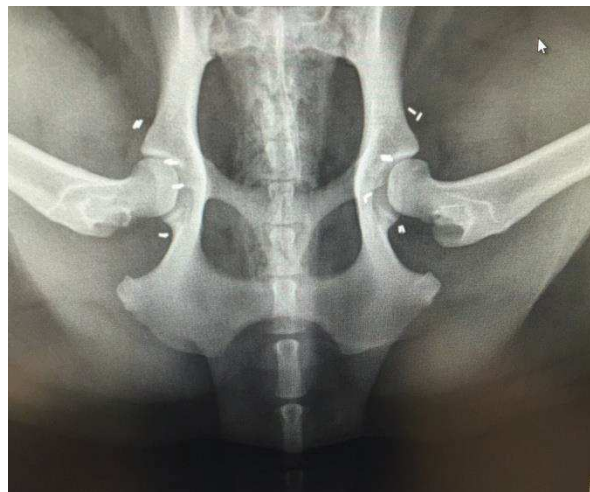


Figure 4 (x-ray picture after the GI)
(Tierärztliche Gemeinschaftspraxis, 2015)

8.3.3 Aftercare

After the GI two more radiographs should be done to control the correct placement of the gold pieces. The positioning of the hip must be equal to the pictures before the implantation to be able to accurately compare the positioning of the gold pieces. A prophylactic antibiotic and analgesic medication can be injected subcutaneously to protect the animal from any kind of infection and to reduce the post operative pain. Recent reports mention that normal aseptical conditions during the implantation are enough to avoid a possible contamination (Jaeger et al., 2012).

9. Survey of GI studies

In the first part of the evaluation of the effectiveness of the GI in general two studies should be examined. The first study was published by Hielm-Bjorkman et al. (2001) and is a double-blinded study over six month. The second study by Jaeger et al. (2007) is in the first six months a double blinded study as well and after this period it was modified to an open follow-up for a further 18 months. The two studies had quite different results and it should be later discussed. The third study is performed by the author himself and the results are presented in study 3.

9.1 Study 1

The first study was performed by Hielm-Bjorkman et al. (2001). This study was carried out as a randomized double-blinded investigation to evaluate the effectiveness of the GI. The total number of dogs was 38 dogs divided into two groups with 19 dogs each. One group was treated with a GI and the other group was a placebo group. The GI group received one gold wire of 2 mm length at each acupuncture point. The skin of the placebo group was just penetrated with a 14 G needle at the acupuncture point and at acupuncture-far-points as well. For localization of the acupuncture points a so called “Point finder”, using the electrical conductivity, was used. The evaluation of the results of the different examinations of the dogs by two independent veterinarians was performed at the day of the treatment and 4, 12 and 24 weeks later. The examination of the dogs was recorded on a video tape and shown to the two veterinarians. During the evaluation the veterinarians tried to scale the lameness and ability to jump off and on a small table and to climb stairs on a scale from 1 to 5. For receiving the grade 1 the dog had to be freely willing to perform the asked exercises. If the dog was completely unwilling to perform the task, or would perform it only with strong encouragement from the owners, it was judged to be grade was 5. The gait analysis was graded from 1 to 5 respectively. The function of the hip joint was examined by the signs of pain during flexion of the hind leg backwards and the range of motion. The owners were questioned at day 0 and in the week 1, 2, 3, 4, 12 and 24. In the two first occasions the owners had to answer a questionnaire about the behavior, locomotion etc. related to pain due to a CHD on a scale from 1 to 5 as well. The signs of pain were scaled from 1 to 10. In this scale a 1 was considered as “showing no pain” and a

10 with the worst signs of pain. The locomotion was scaled from 1 to 10 by the owners too. The result of this study showed no significant difference between the GI treated and the placebo group. However, both group showed a significant improvement compared to the situation before the procedure with $p = 0.036$. The GI group had an improvement of 65% and the placebo group of 53%. The difference between the two groups was with $p = 0.19$ not significant. The owners detected in the GI treated group an improvement of pain of 53 % and in the placebo group an improvement of 63 % with $p = 0.0001$ for the GI group and 0.0034 for the placebo group which was considered as significant towards the situation before the intervention. However, the difference between the two groups was also not significant. Even after 12 and 24 weeks after the treatment (gold or placebo) no significant difference between these two groups could be detected.

9.2 Study 2

The second study was for the first six month a double-blinded placebo controlled clinical trial done by Jaeger et al. (2007). After the period of six month the clinical trial was changed and an open-up study followed for additional 18 months. The aim of this study was to examine the pain relieving effect of the GI over a period of 24 months altogether. During the first six month the dogs were divided into two groups. The placebo group consisted of 42 dogs. The group receiving a GI treatment contained 38 dogs but two dogs dropped out during the first six month. After the double-blinded trial ended at six month 73 dogs were studied for additional 18 month. To the owner of the previous placebo group it was offered to perform a GI. According to that in the following 18 months the study consisted of three groups. The first group was the previous GI group called GG (gold gold), the second group the previous placebo group receiving a GI treatment after the six month called PG (placebo gold). These two groups together were also examined as a pool group (GG + PG). In the last group were the dogs which were previously in the placebo group and didn't receive a GI treatment after the end of the double-blinded study. This group was called PC (placebo control). The animals withdrawn from the study due to reasons related to the investigation remained in the analysis till the last observation. Before the animals received any treatment (placebo or GI) the owners were asked to score the pain of their dog from 0 (no pain) to 10 (extreme pain) and the behavior with a scale from 1 (deterioration) to 6 (no signs of dysplasia). At the same time the professional clinical

investigator scored the animals also according to their hip pain into a 4-point scale for each hip side and subsequent added into a total score. The number 1 was “no pain” and the number 4 coded extreme pain reactions. After the 24 month period the results of the investigator and of the owner were more or less similar. The pooled group (GG + PG) showed a reduction in pain. This reduction was significant with $p < 0.01$ in both scoring systems (owner and clinical investigator). In the PC group the investigator examined an increase in the hip pain from 4.4 to 5.0 in the total hip pain score. This increase was not significant with $p = 0.28$. The owner of the PC group graded the hip pain from 4.4 before the start of the investigation to 3.0 after the 24 months with $p = 0.06$. The p-value showed that the reduction detected by the owner of the PC group was not significant. To the question regarding the behavior the pooled group showed an increase of 81.8 %. The increase towards the PC was significant with $p < 0.001$. The difference between the PG and PC group with $p = 0.03$ it was also significant. The behavior in the PC group was described from moderate improvement to moderate deterioration after the 24 month. The dogs showed a further improvement from six month and 24 months. In the first period of the investigation the improvement was 85.3% and after 24 months it reached 94.1%.

9.3 Study 3

9.3.1 Materials and methods

9.3.1.1 Study design

This study was designed as a simple open study over two years in the scope of this thesis. The dogs all suffered from CHD and showed signs of pain already. The diagnosis of CHD was affirmed through a thorough lameness and radiologic examination. The effect of the pain relieving effect of the GI was collected via questioning the owners. Randomly the results of the questioning were compared with the aftercare examinations of the veterinarian. The comparison showed that the answers of the owners corresponded more or less with the results of the examinations by the veterinarian. Because of the large group of patients extreme opinions unrelated to the treatment were statistically compensated itself. On this basis it was possible to get an objective mean value of the owner’s evaluation.

9.3.1.2 Animals

The total number of dogs treated with the GI was 83 at the beginning. After the period of two years only 65 dogs were still alive. Two dogs were euthanized because of diseases not related to the treatment (withdrawals). Eight dogs died due to their age and the rest discontinued because of unknown reasons (drop outs). The animals belonged to 30 different breeds listed in table 2.

The average body weight was 31.53 which were similar to the body weight of the patients in the above examined studies. The average age of the dogs was 6.33 with a range from 0.8 years to 12.8 years. Four dogs were not included in the survey due to the fact that the GI was done for prophylactic reason before any signs of pain were visible. However the radiological examination showed that they had a high risk of suffering from pain due to CHD in the future. At the end the results of these four animals should be mentioned briefly.

Poodle	2	Weimaraner	1
Vizsla	1	Rhodesian ridgeback	2
Fox Terrier	1	German shepherd	11
Maltese	1	Bernese mountain dog	7
Beagle	1	Appenzell mountain dog	1
English toy spaniel	1	Boxer	3
Small munsterlander	1	Dogue de Bordeaux	2
Border terrier	1	Italian greyhound	1
Flat-coated retriever	1	Great schnauzer	2
Staffords1hire bull terrier	1	Airdale terrier	2
Hovawart	2	Bouvier des flandres	1
Sheltie	1	Australian shepherd	3
Alaskan husky	2	Bulldog	2
Mix breed	7	Malinois	1
Carlin	1	Labrador	20

Table 2 (breeds and their numbers of dogs)

9.3.1.3 Questioning

To evaluate the pain relieving effect of the GI the owners were asked to rank the degree of pain before the GI treatment on a scale from 1 to 10. The number 1 meant that the dog was showing no signs of pain at home. Corresponding to it the number 10 was given if the dog showed drastic signs of pain such as the inability to get up after lying down, inability to climb stairs, strong pain during flexion etc. The degree of pain after one week, six months and two years were ranked in the same way. Furthermore, the owners were questioned about any medication of the animals before and after the GI as well as their dosage and their indications. At the end of the questioning the owners were asked about any change of the general behavior of their dogs after the GI. The answers were not coded in a scale to give the owners the possibility to describe the detected changes in their own words.

9.3.1.4 Clinical procedure

The GI was performed in the clinic Heynck & Partner in Borken in West of Germany. The diagnosis of the CHD was confirmed several days before the GI was performed. On the day of the implantation the dogs were anesthetized with a combination of xylazin, ketamine and diazepam. Two additional radiographic pictures were made shortly before the implantation took part. For the first picture the course of beam was latero-lateral; for the second picture it was ventro-dorsal. A certificated gold acupuncturist performed the GI on the four points mentioned above (GB 29; GB 29.5; GB 30; GB 31) under aseptic conditions to avoid any infection. During the implantation the veterinarian took special care to check for any leakage out of the cone of the needle. After the implantation two further radiographic pictures were done to control the correct placement of the gold beads. No antidotes for the anesthetic drugs were given to terminate the narcosis. To reduce the post operative pain metamizolium natrium with a half life of 4 to 5 hours was injected to each dog as well as an antibiotic. The first consultation after the GI was after two days to control the healing of the small incision wounds as well as to evaluate a first effect of the GI. The second consultation was approx. one week later. Further visits were arranged individually with the owners depending on the improvement of the dogs.

9.3.1.5 Statistical methods

All continuously distributed variables were reflected as mean values of the population with CI of 95%. The Interval was calculated according the Student procedure. The comparison within the group was statistically tested with a two-tailed one sample t-test. The initial score stated by the owner's answer were the covariate. The level of significance was set with α -error $p < 0.05$ (Marusteril and Bacarea, 2010). All statistical values are represented in the tables below (table 3 to 7).

total number of dogs at day 0	83
age (years)	5.98 (5.31-6.64)
weight (kg)	31.62 (29.2-34.03)
pain	6.93 (6.81-7.04)

Table 3 (data of the dogs treated with GI in mean)

9.3.2 Results

The questioning recorded that the mean pain score due to CHD was 6.93 (CI 6.81 – 7.04) (table 3) before the implantation. But the single scores ranged from 10 to 2. After one week the mean score decreased to 3.71 (CI 3.19 – 4.24) meaning a decrease of 46.4%. This decrease was significant with $p < 0.0001$ (table 4). However a detailed study of the results showed that the changes in the coded degree of pain had a wide individual range from 9 to -1. 84.3% of the dogs showed an improvement (minimum 25% reduction) and 43.4% of the dogs had a great improvement (more than 75% reduction) of hip pain due to CHD (table 5). 19 dogs even showed no signs of pain anymore. The mean score of these 19 dogs were slightly lower than the mean score of the total population (5.76 compared with 6.93). On the other hand some dogs showed no improvement at all after the period of one week. The pain score of three dogs even rose, meaning deterioration. However the rise was mild and the pain score increased by just 1 point. After six month the mean score decreased further to 2.11 (CI 1.80 – 2.42) equal to a decrease of 69.5% compared to the mean value before the implantation. Compared to the values after one week it showed a significant decrease in the mean value with $p < 0.0001$ and a percentage of 43.2%. Furthermore, the statistical analysis indicated that the individual differences lessened within the population after six month. Of the three dogs showing deterioration at the first week two dogs were

improving now. The other dog had further deterioration. The percentage of dogs showing improvement (minimum 25% reduction) increased to 92.6% and the percentage of the dogs with great improvement (minimum 75% reduction) was 75.3% after six months. Two years after the GI the mean of the pain value remained more or less constant at 2.1 (CI 1.72 – 2.47). This change had to be considered as not significant with $p = 0.3881$. The differences within the population were more pronounced again compared to the values after six month. But compared to the values of the fist week the standard deviation was still lower (1.5 compared to 2.4). The dogs showing a great decrease in pain compared to the day before the GI procedure were 78.5% of the group; dogs with minimum 25% reduction in pain had a percentage of 95.4%.

	day 0	1 week	6 months	2 years
number of dogs	83	83	81	65
pain (mean)	6.93 (6.81-7.04)	3.71 (3.19-4.24)	2.11 (1.80-2.42)	2.1 (1.72-2.47)
reduction (to day 0)	6.93	3.21	4.82	4.83
reduction in %		46.4%	69.5%	69.7%
reduction (to before)	6.93	3.21	2.11	0.01
reduction in %		46.4%	43.2%	0.6%

Table 4 (reduction in pain)

	1 week	6 months	2 years
min 25%	84.3%	92.6%	95.4%
min 50%	66.3%	91.4%	92.3%
min 75%	43.4%	75.3%	78.5%

Table 5 (improvement compared to day 0)

At the end the results of the four dogs treated with GI in the meaning of a prophylactic therapy should be evaluated. The data of these four dogs are visible in table 6. The average body weight was 32.25 and the average age 2.95. None of the dogs showed any signs of hip pain. Therefore the degree of hip pain was given with 1. The radiographic pictures however showed that degenerative processes were already present in the hip joint, indicating a CHD with secondary cox-arthritis. The GI was performed as a prophylactic therapy with the aim in prevention of prospective pain. The data recorded that after two years these four dogs showed still no signs of pain, as it was desired.

number	weight (kg)	age (years)
1	44.5	3.5
1	30	4
1	29.5	3.5
1	25	0.8
total = 4	mean = 32.25	mean = 2.95

Table 6 (data of the dogs treated prophylactic with GI)

The data (table 7) regarding the medication before the GI showed that 33 dogs were treated with NSAIDs. After one week in 25 cases the owner had to give still NSAIDs though six dogs out of these 25 got only half the dosage as before. After six months 7 dogs were treated additionally with NSAIDs to this time. Five of them were treated with a dosage 50% less than previously. After two years from these 33 dogs only four got NSAIDs additionally to the GI. However in one dog the dosage was further decreased to a quarter of the previous dosage. In a second case the maintenance dosage was half of the original dosage and the two other dogs got the same dosage as before the GI due to the deterioration of the general status mentioned above. The records about additional medication showed that in older patients the owner gave additives on the basis of chondroitinsulfate, glucosamines and other homeopathics but no NSAIDs.

	dosage	day 0	1 week	six months	two years
carprofen	1/1	21	13	1	1
	1/2	0	5	4	1
	1/4	0	0	0	1
firocoxib	1/1	12	6	1	1
	1/2	0	1	0	0
	1/4	0	0	1	0
total		33	25	7	4

Table 7 (number of dogs treated with NSAIDs and the dosage)

10. NSAIDs

In the COA the inflammation and pain are primarily mediated directly or indirectly through the action of eicosanoids resulting in the production of prostaglandins and thromboxane. To achieve pharmacologically the aim of a palliative therapy in arthritis the most commonly used drugs since 1899 belong to the group of the NSAIDs. Common for all drugs of the NSAIDs is the inhibitory effect of the synthesis of prostaglandins through the inhibition of the two isoforms of the endoperoxidase H which transforms arachidonic acid into prostaglandins. These two isoforms are called Cox-1 and Cox-2. However is the ratio of Cox-1/Cox-2 inhibition different in the single drugs (Brooks and O Day, 2000; Tegeder et al., 2001; Dannhardt and Kiefer, 2001; Pollmeier et al., 2006).

10.1 Cox-1

Mainly the cyclo-oxygenase-1 is responsible for the physiological production of prostaglandins from eicosanoids (basic level) and is expressed in nearly all kinds of tissues in different organs like the stomach, intestines, kidneys, platelets etc. The produced prostaglandins play a role in the protection of the gastric and duodenal mucosa, the control of the renal blood flow, the vascular haemostasis, the ovulation, implantation and parturition as well as in the bronchodilatation in the lungs (Brooks and O Day, 2000; Dannhardt and Kiefer, 2001; Tegeder et al., 2001; Pollmeier et al., 2006).

10.2 Cox-2

Before 1980 it was believed that only one type of Cox exists. 1991 a hypothesis of another isoforms was validated (Tegeder et al., 2001; Dannhardt and Kiefer, 2001; Pollmeier et al., 2006). Earlier investigations could trace only the mRNA of Cox-2 enzymes in the above mentioned organs and not the enzyme itself which is why it was believed that the Cox-2 enzyme was expressed in inflammatory processes (Pollmeier et al., 2006). Other later articles described an up-regulation of Cox-2 in the peripheral tissue and spinal cord after an injury (Tegeder et al., 2001). This indicated a role of Cox-2 as a primary pro-inflammatory enzyme inducible by different mediators (serum growth factor, cytokines and mitogens). Newer investigation showed that the activation of the Cox-2 enzyme was responsible for

an excessive production of prostaglandins from eicosanoids as it was mentioned before. Due to this increased production a sensitization of nociceptors took place leading to an increased release of inflammatory mediators (Dannhardt and Kiefer, 2001; Pollmeier et al., 2006). Further investigations could then detect an additional non-inflammatory role of the Cox-2. The physiological action of the Cox-2 enzyme is involved in the renal function by acting at the rennin-angiotensin system, healing of ulcers, reparation of bones and the reproduction in female organisms. However most of the Cox-enzymes belong to Cox-1.

10.3 Classification of NSAIDs

According to the different ratio of Cox-1/Cox-2 inhibition the NSAIDs are classified into three groups. The difference in the ratio is generated through the larger binding site of Cox-2 caused by a variation of the molecular structure (Dannhardt and Kiefer, 2001). In the first group the drugs which are non selective for Cox-1 or Cox-2 enzyme are included. They have a relative narrow therapeutic index and can easily cause gastric ulcers, indigestion, damage in the liver and the kidney, prolongation of the bleeding time, cardiac failure and reproductive problems (Brooks and O Day, 2000; Tegeder et al., 2001; Pollmeier et al., 2006). The second generation of NSAIDs is more selective to inhibit Cox-2. The therapeutic index is larger than for the first generation. However the potential adverse effects typically for NSAIDs can still occur during the treatment. The most selective NSAIDs are of the third generation (coxibs) like ibuprofen, naproxen etc. (used in the human medicine). For veterinarian purpose firocoxib was specially designed and is used only for the treatment of animals. The therapeutic index of this class is the broadest with a much lower incidence of adverse effects. Investigations showed that the in vivo therapeutic level is below the necessary level of in vitro inhibition of the Cox-1 enzymes (Brooks and O Day, 2000; Pollmeier et al., 2006). However, the risk of adverse effects increases in all classes with the age and the dosage. This increase in the risk can lead to serious problems in the long-term treatment of older patients (Brooks and O Day 2000; Dannhardt and Kiefer 2001). To counteract the adverse effects an additional treatment with corticosteroids, anticoagulants and drugs for the protection of the gastric mucosa will then be necessary. Another serious problem could be the interaction with other drugs and the inhibition of the cytochrom P 450 in the liver which causes a change of the metabolism of other drugs (Brooks and O Day, 2000).

10.4 Study A

The study A was designed by Pollmeier et al. (2006) as a randomized double-blinded study to compare the pain relieving effect of firocoxib and carprofen in the COA. The time frame of the study was set by 30 days. Criteria for this study were that the dogs suffered from COA in minimum of one or more joints; it was not limited to CHD. The COA was proved by a radiographic and lameness examination. The dogs had to be lame for at least four weeks before the start of the study. Dogs treated with NSAIDs or glycosaminoglycans seven days before the start or treated with corticosteroids within the period of the study (30 days) were not included in the investigation. Dogs operated 14 days previously to the study were also not enrolled in this study. The total number of 218 dogs was divided randomly into two groups. Group 1 (108 dogs) was treated with carprofen and the second group (110 dogs) was treated with firocoxib. The mean body weight was more or less equal with 31.1 kg for group 1 and 30.6 kg for group 2. The mean value of the age was 8.5 and 8.7 years respectively. The dosage of carprofen was at least 4 mg/kg and for firocoxib at least 5 mg/kg. The way of administration was orally in 24 hours interval. At the initial day (day 0) the dogs were physically examined by veterinarians (table 8). In the same way a physical examination was performed after two weeks and one month. During the examination the overall lameness, pain on manipulation and palpation, range of motion and the swelling of the joint were evaluated and the results scored from 0 to 3 (0 = best results; 3 = worst results). Except the overall lameness the results were assigned to the most affected limb / joint. On the base of the physical examination an overall score was designed too. To calculate the overall score the values of 2 x lameness, pain on manipulation / palpation, range of motion and the swelling of the joint were added together. Additionally the owners were asked to scale the weekly improvement of their dogs compared to the initial day from 0 to 3. Great improvement was coded with 0 and no improvement with 3 (table 9). The owners had also to write a dairy about any changes in the behavior and recognized adverse effects related to the treatment. At the end of the study the owners evaluated the palatability and the convenience of administration of the tablets. To simplify the subsequent comparison of the effect of the GI with the effect of classical pain treatment with drugs only the results of the overall score and the results given by the owners should be mentioned in the text. However the complete results of the physical examination are shown in table 8. The overall score evaluated by the veterinarians showed that after two weeks 92.4% of group 1 and 92.5% of group 2 improved. At the end of the study the

number of dogs improving in the overall score changed to 92.4% (group 1) and 93.4% (group 2). The evaluation by the owners showed that the improvement compared to the initial day in group 1 was lower than in group 2. Also the rise of the effect was faster in the second group. At the first week 77.1% of the owners of the dogs in group 1 and 81.1% of the owners of the dogs in group 2 evaluated that their dog showed an improvement. These percentages increased until the second week and thereafter remained more or less constant (92.4% for group 1 and 96.2% for group 2). However, when comparing the results of dogs which improved greatly (more than 75%) the results of the two groups showed a significant difference with $p = 0.0439$.

	carprofen		firocoxib	
day	14	30	14	30
overall score	92.4%	92.4%	93.4%	92.5%
pain on manipulation	81.0%	85.7%	86.8%	86.8%
joint swelling	13.3%	20.0%	11.3%	13.2%
range of motion	36.2%	44.8%	44.3%	50.9%
improved	75.2%	83.8%	78.3%	84.9%
greatly improved	24.8%	30.5%	36.8%	55.7%

Table 8 (results of the physical examination by the veterinarians in % of total dogs) (Pollmeier et al. 2006)

	days	7	14	21	30
improved	carprofen	77.1%	93.3%	93.3%	92.4%
	firocoxib	81.1%	92.5%	95.3%	96.2%
greatly improved	carprofen				50.5%
	firocoxib				60.4%

Table 9 (results of the evaluation by the owner in % of total dogs) (Pollmeier et al. 2006)

50.5% of the dogs treated with carprofen (group 1) and 60.4% treated with firocoxib (group 2) showed a great improvement. The palatability was evaluated with 61% and the convenience of administration with 90%. Concerning the adverse effects 31.5% of the owners in group 1 recognized a minimum of one health problem. In group 2 the dogs showing a minimum of one health problem were at a level of 22%. However an examination done by the veterinarians judged the adipsia, anorexia, diarrhea, emesis and polydipsia of only 8 cases (7.5%) related to the treatment with carprofen. In the group 2 only the emesis of two dogs (1.8%) were considered to be related to the treatment with firocoxib.

11. Discussion

The results of the different studies showed that the GI had an analgesic effect. The third study alone showed that the implantation of gold achieves its greatest effect after a certain time. After one week the owner evaluation recorded a reduction in pain mean value of 46.4% and later by the time of 6 months a reduction of 69.5% compared with the mean value before the GI. Also the results of the degree of pain at six months compared to the results after one week showed a significant reduction. This could be explained as being the time needed for the potential effect of the gold itself. It is possible that the period of one week is too short for the phagotizing cells to liberate enough gold from the gold beads and to transform it into aurocyanide. The answer of some owners about the complete disappearance of pain of the GI was surprising. It would be interesting to know if this great effect of the GI in these dogs at the first week was due to an acupuncture effect or through the effect of the gold. The answer of several owners that the effect of the GI was immediate suggests that there is a certain effect from the acupuncture itself and not from the gold alone. That the effect was not visible in all dogs could be due to the fact that the acupuncture points were not localized with the help of a point finder exactly. The great effect of the GI in the first period should be investigated in further studies with the aim to optimize the performance of the GI. The evaluation showed also that the mean of the pain score slightly increased between six months and two years. But this change was not significant with $p = 0.3881$. However, a more detailed examination of the results showed that in the older dogs the degree of pain was increasing again. Assuming the results as a future trend a possible reason could be the advanced age and the long history of CHD in

the animals (at the end of the study the dogs were nine years or older). Considering that the GI is not a curative therapy the further degeneration of the hip joint was not stopped. With a higher degree of degeneration due to CHD it is possible that the pain relieving effect of the GI alone was not sufficient anymore. The data of the prophylactic GI therapy showed great effect if the non-occurrence of pain was considered as a positive result. To which extend the GI therapy is responsible for the non occurrence of pain over the time was difficult to say. CHD does not provoke in pain general and if it does the degree is highly individual as mentioned before. For a proper investigation the number of dogs treated with a prophylactic GI therapy was also too small to be able to detect more than just a possible trend. Comparing study 3 with the two other GI studies (Hielm-Bjorkman et al., 2001; Jaeger et al., 2007) it showed that the success rate of the second and third study were much higher than in study 1. The less favorable results from study 1 could be due to the fact that the veterinarians were evaluating the examinations of the dog from a video tape. It was mentioned that the veterinarians found it difficult to evaluate the improvement of the dogs without seeing the dogs in reality. Additionally a difference in the method of performing the GI could be detected. In the first study only one gold bead was used for each treated point (acupuncture and trigger point) whereas in the two other studies two beads per one point were always used. A higher amount of implanted gold could cause a higher effect in the surrounding tissue (Yanni et al. 1994; Danscher, 2006; Larsen et al., 2007). The great percentage showing deterioration in the first study is also remarkable. 29% of the dogs treated with gold and 18% of the untreated showed deterioration. In the second study no dog (0%) showed deterioration. In the third study only 1 dog out of 81 (1.2%) showed deterioration after six months. Possible reason to the lower success rate could be that during the GI performance the joint capsule was possibly penetrated and a gold bead was put within the capsule leading to great pain. The possible danger of an insertion of gold was recorded by 36.8% per each dog (Jaeger et al., 2012). The control of a radiographic examination mentioned in the study would be not enough to exclude a potential insertion of gold into the joint (capsule is not visible in x-ray pictures). It could show only that the gold beads were not moving away from the insertion point. Also the fact that the treated group shows a higher rate of deterioration than the untreated group suffering just from the progression of the degeneration of the hip joint alone gives us a suspicion of an incorrect performance of the GI. Another possible explanation of the higher rate of deterioration in the treated group could be the small number of dogs in each group. Transforming the percentages into real numbers the difference of the deterioration of the two groups was

made by 2 dogs. In general the second and third studies were quite similar. The total number of dogs treated with a GI from study 2 and 3 were more or less equal. At each treated point two gold beads were inserted and during the procedure of the GI any serum leakage was carefully monitored to avoid any accidental insertion of gold into the joint. At the end a radiographic picture controlled the correct placement close to the joint of the gold beads. The assessment of the owner of the pain after two years showed that in the study from Jaeger et al. (2007) the degree of pain was in mean 2.4. In the third study the owner assessed the degree of pain with 2.1. This leads to the conclusion that the reduction in pain in the third study would be significant compared to a potential placebo group too. The difference between the studies from Jaeger et al. (2007) and the study in the scope of this thesis is that in the second study the owners detected a bigger improvement from six months to two years. However, after six months the percentage of dogs improved was higher in the third study. After six months of treatment the owner from the second study recorded at 85.3% of the dogs an improvement and in the third study it was 92.6%. At the time of two years the percentage of dogs improving increased in both studies. However, the increase in both studies was calculated as not significant. In summary we can say that the second and third study came to quite equal results. It is interesting that in the two investigations from Hielm-Bjorkman et al. (2001) and from Jaeger et al. (2007) the results for the placebo group were more or less equal. The two placebo groups showed an improvement of more than 50% which is higher than a normal placebo group should show. A possible weak point in these two studies is that the skin of the dog was penetrated with metal needles at the acupuncture points and acupuncture-far points. Therefore a potential acupuncture effect cannot be excluded completely. Investigation showed that a normal acupuncture in human medicine can show an effect from 1 week up to 2 months or more (sometimes even years) (Helms, 1998). Other studies in rats showed that acupuncture can also cause an effect far-away from the point of insertion (Langevin et al., 2001) which is why it is possible that the insertion of the needles away from the acupuncture points (study of Hielm-Bjorkman et al., 2001) could also cause an analgesic effect. Additionally a survey of several studies showed that studies investigating the pain relieving effect of a treatment and using a placebo group as a control group the effect of the placebo was always higher than in other studies. The general percentage showing an effect to placebo was from 30% to 40%. In the two studies mentioned above the placebo effect was recorded as 50% to 60%. Furthermore, it showed that the percentage showing a placebo effect to a treatment

was higher in studies with a low number of participants (Hróbjartsson et al., 2001). This could be a reason why the placebo group in the first study from Hielm-Bjorkman et al. (2001) had such a great effect on the final results. The total number of dogs in this study was 38 dogs divided into two groups with 19 dogs in each. The second study had 42 dogs in the placebo group at the beginning. This number of participants would be big enough for a placebo group but no data was available before the randomization code was broken. After the opening of the study the placebo group consisted of 7 dogs only. Another potential reason for the good results in the placebo groups could be due to the fact that the owner visited the clinic several times. It was mentioned that it could be possible that they finally followed the repeated general advice of the veterinarian such as reduction in weight, physiotherapy etc. To compare the third study with the investigation of the effectiveness of NSAIDs by Pollmeier et al. (2006) the data had to be transformed to one equal grading system for both studies. In the study A the grading system was from 0 to 3. Transformed to percentages an increase by one grade in that study would be equal to an improvement of 25% or more in the third study. The results showed that carprofen needed a time of approx. 14 days and remained constant by 92 – 93% of dogs improved. The amplitude of the positive effect of firocoxib showed a steeper incline. After one week 77.1% of dogs in the carprofen group have improved. The firocoxib group and the GI group (study 3) showed more or less equal results (81.1% and 84.34%). At the final stage the results for improved dogs in the 3 groups were from 92% to 96%. In the gold group it was reached between 6 months and two years after the treatment whereas in the two other groups it was at 30 days after the treatment. The exact time of the final stage of a GI however remains unclear. The data from the third study showed the effect only at the time of six months but it is possible that the final stage was reached much earlier. To detect this final stage closer observation intervals would be useful in future trials. According with the presumption that 1 grade means 25%, dogs greatly improved (rise by 2 grades in the study A) had to be seen equal with dogs showing 75% or more improvement (study 3). In the study A from the caprofen group had 50.5% dogs greatly improved. The firocoxib group however had 60.4% and the gold group 78.5%. It seemed that the gold group had a much higher percentage of dogs greatly improved than the other two trials. A possible reason for the excellent results of the gold group could be that many dogs were treated with NSAIDs before the GI was performed and didn't need further medication anymore. This could evoke a more positive evaluation of the effect of the GI. Especially the owners of dogs with high ages at the time

of the GI could evaluate the effect as great. It is possible that these dogs suffered in the past from some adverse effect related to treatment with NSAIDs. The fact that no further treatment or treatment with a lower dosage of NSAIDs was necessary after the GI could provoke this good result in the assessment of the owners. Another weak point of the third study is that it was not blind. The owners could rate the improvement too high knowing that their dogs got a GI. Therefore it would be useful in later trials to investigate also the results of examinations done by veterinarians. Analyzing the way of action of the GI and firocoxib it shows that both types of therapy reduce at the end the amount of prostaglandins produced by Cox-2. The GI therapy affects the production of cytokines and other mediators reacting on the Cox-2 enzymes while the coxibs (e.g. firocoxib) have the enzyme as a direct target. In both types the amount of the final production of prostaglandins is reduced by sparing the important Cox-1 enzymes. The non-stimulation of Cox-1 leads to fewer or no adverse effect. Carprofen on the other side is less selective for Cox-2 as mentioned above having a greater risk of adverse effects.

12. Conclusion for the daily praxis

It was shown that the GI had an equal range of effectiveness as the therapy with firocoxib without causing adverse effects. Both therapies achieve relief in pain by reducing directly or indirectly the production of prostaglandins. The advantage of the GI compared to the treatment with carprofen is that the Cox-1 enzymes are spared and no adverse effects typical for NSAIDs occur. It was also shown that the inhibition of Cox-2 through firocoxib can cause adverse effects. The benefit compared to any surgical intervention is that the GI is a minimally invasive technique whereas the classical surgeries are invasive. For the owners it could be also beneficial that they do not have to give any tablets after a GI. The owner quoted the palatability with 61% (meaning that for 39% it was not palatable) and the convenience of administration with 90%. Another benefit for the GI could be that the owners do not have to go or drive monthly to the clinic to buy tablets. In summery it can be said that the GI can be a good alternative, or addition to classical pharmacotherapy. It helps to avoid the administration of NSAIDs or to reduce the dosage. However for the daily routine in the veterinary praxis it would be interesting how great the incidence of other diseases like cruciate ligaments rupture or other dysplasia are in the investigated breeds. Most of the treated dogs in the different studies were large sized dogs. These dogs are also prone to suffer from the other mentioned diseases. The GI is only locally effective whereas the NSAIDs have a systemic effect. In dogs suffering not only from CHD but also from e.g. an elbow dysplasia (ED) a careful therapy with firocoxib could be therefore more advantageous.

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HuVetA relies on the latest technology in order to provide easy searchability (by search engines, as well) and access to the full text document, whenever possible.

Based on the above, HuVetA aims to:

- increase awareness of Hungarian veterinary science not only in Hungary, but also internationally;*
- increase citation numbers of publications authored by Hungarian veterinarians, thus improve the impact factor of Hungarian veterinary journals;*
- present the knowledge base of the Faculty of Veterinary Science, Szent István University and its partners in a focussed way in order to improve the prestige of the Hungarian veterinary profession, and the competitiveness of the organizations in question;*
- facilitate professional relations and collaboration;*
- support open access.*

***SZIA Szent István Archive** is the online repository of scholarly publications affiliated with the Szent István University.*