FOUR-LEGGED PROLOTHERAPY

A Case for Prolotherapy and Its Place in Veterinary Medicine

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ABSTRACT

Pain management and the resolution of that pain has become the campaign of the current veterinary and pet owner communities. The fastest growing segment of our pet population is the aging dog and cat. Prolotherapy is one of the oldest, yet little known, modalities for resolution of pain and lameness. Prolotherapy is compared to its pharmacologic and surgical counterparts. This paper contrasts the current practices available for the resolution of common (ACL) knee injuries and (HD) hip dysplasia in the veterinary community. ACL injuries and HD are the two most prevalent and costly pathologies in modern veterinary practices across America. The science of Prolotherapy is brought into focus and compared with conventional solutions for soft tissue injuries and osteoarthritis. Risk factors and complication statistics are brought to light. The objective of this paper is to make a case for Prolotherapy and emphasize its usage and application in veterinary medicine.

It is concluded that Prolotherapy is an excellent medical option that diminishes pain and resolves clinical signs of lameness. Prolotherapy is a viable alternative to surgical options and curative in many cases of ACL and HD pathologies. Prolotherapy is also a marvelous tool in conservative treatments in animals with unresolved pain, osteoarthritis and lameness issues. Prolotherapy is a great post surgical option to eliminate chronic pain and accelerate rehabilitation in our animal community.

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Introduction

WHY WE NEED PROLOTHERAPY

Animal hardship and pain is a universal problem and awareness of it has risen steadily over the past 20 years. Public pressure has galvanized oversight and Institutional Animal Care and Use Committees (IACUC) to prevent and minimize pain and distress in animals used in laboratory research all over America. Unmitigated animal pain across species is a well-publicized and appreciated issue among the general public. Beginning in the 1990s, there was a renewed focus in veterinary schools to teach pain management. This was in part driven by client concerns for their pets and demand for additional medical options for common conditions. A shared concern over animal pain enters every aspect of a veterinary practice. It is important that veterinarians recognize when their patients feel pain, so that they can intervene. It has also been recognized that the client is happier when their pet animal is not in pain.[1]

The University of Pennsylvania recently published the Canine Brief Pain Inventory (CBPI questionnaire).[2] The CBPI questionnaire is an eleven question, basic numeric rating system to assess the severity of the pain in our companion canine animals. This is an owner-completed questionnaire and has proved successful in randomized studies.[3] There have also been other attempts to measure chronic pain with structured questionnaires. These questionnaires attempt to measure effects on health-related quality of life issues with the goal that the results would support a method of improving clinical decision making, facilitate development of evidence-based therapeutic options for chronic diseases, and help veterinarians and owners define humane end points in the canine patient. Information gained would provide improved measurements of clinical change in animal studies that use dogs with naturally occurring orthopedic chronic pain to evaluate novel human treatments.[4]

Osteoarthritis is a large problem in the veterinary community. When the FDA approved NSAIDs (non-steroidal anti-inflammatory drugs) for canine use in 1995, a typical veterinarian's practice was made up of 20% geriatric animals. Currently, it is over 25%.[5] Although age is not a disease, the geriatric pet population often suffers from degenerative and painful conditions. Osteoarthritis is a common cause of pain in our human population, and the focus of active research for pharmaceutical intervention.

In addition to a better understanding of human medical conditions shared with companion animals, there is a growing wealth of studies focused on methods to recognize and alleviate pain wherever possible in lab animal research. As our own pets age in our homes, we are the primary witness and have to interpret and relay their medical signs to veterinarians. The pain pathways are similar in cats, dogs and humans, the supposition can be made that if it hurts us, it hurts them.[6] We address the many signs of pain to monitor our pets and present traditional pharmacological and surgical options, as well as a viable emerging therapy. Prolotherapy is a viable solution for controlling pain within our pet population. It is useful for both chronic arthritis and acute ligament and tendon injuries and laxities all over the body. In this article, we will focus on the most common indications and methods for employing Prolotherapy in small animals.

Pain

THE PERCEPTION, THE ALLEVIATION AND THE DRUG ALTERNATIVES TO PROLOTHERAPY

Osteoarthritis is a costly and significant problem in dogs, cats, horses and humans.[7] It is a complex syndrome affecting joints, an estimated 20% prevalence of dogs over one year of age are affected and suffer pain and disability as a result.[8] Animals perceive pain and suffer just like humans.[9] Continuing flare-ups in diseased joints can cause chronic pain. Older pets are the primary population affected by osteoarthritis, and many of them are also obese. Dogs usually present with lethargy and lameness. Cats do not normally walk on a leash, and their lameness can remain unnoticed. Cats usually exhibit their pain with behavioral changes. Pain in the osteoarthritic patient can be constant, but the signs are often most pronounced when pets take their first few steps after resting. As veterinarians, we know that radiographs do not always correspond to the level of pain.[10] Sometimes the symptoms are subtle, and many times owners do not realize that their dog or cat has arthritis. Pet owners think that their animals are merely slowing down. Cats are great at hiding their pain. It benefits the animal, when both the veterinarian and owner recognize developing symptoms early. Pain is ultimately the consequence of arthritis, and it is important to assess the arthritic patient on a frequent basis in order to properly evaluate, and quantify a pain score.

Common signs of pain-related behavior in dogs and cats:

- Increase in anxiety- sometimes showing agitation or rapid breathing
- Decrease in social interaction
- Increase in aggressiveness
- Diminished performance, they don't want to go as far or as fast
- Changes in temperament
- Abnormal gait and body position
- Eating less, with a resulting loss of weight
- Decreased activity with weight gain
- Inappropriate elimination in the house
- Excessive chewing, biting, or licking of an area or limb
- Difficulty in walking, climbing stairs, or getting in and out of the litter box or car
- Resting more than usual
- Difficulty getting up from a lying position
- Failure to self groom
- Slow or stiff movements upon waking, after a rest, or in cold weather
- Limping
- Swollen joint(s) warm to the touch
- Personality changes such as your pet no longer likes to be touched
- Reluctance to walk, run, climb/descend stairs, jump, or play
- Lagging behind on walks
- Reluctance to extend rear legs
- Sluggishness
- Inability to stretch
- Vocalization on handling
- Unwillingness to play with other pets

As a general rule, a dog that is seven years old can be considered mid-age to senior. Older pets should be screened for signs of osteoarthritis and lameness, as well as assessed for significant changes in weight and

body condition. The obesity epidemic amongst animals predisposes our pet population to health problems and shortens their life span.[11]

Lameness is hard to identify. Some signs are:

- Difficulty getting up and sitting down
- Hesitation at stairs and, in the case of cats, hesitation in jumping
- Shifting weight, even when eating
- One paw is bigger than another, indicating a chronic weight shift for comfort
- Muscle atrophy

All of these results of pain are serious and potentially harmful by causing the breakdown of other metabolic systems in the body. The typical veterinary approach to managing osteoarthritic pain has focused on medical and surgical treatments that often fail to correct the underlying cause.

Some of the potential responses of the body to pain include[12]:

- Decrease in peripheral blood flow
- Altered metabolism and an up-regulation of cortisol
- Decrease in GI motility
- Suppression of the immune system
- Impairment of wound healing
- Reduced respiration and risk of pneumonia
- Development of a chronic pain syndrome

CONVENTIONAL PHARMACOLOGIC TREATMENTS FOR CHRONIC PAIN

Many traditional practitioners first prescribe either non-steroidal anti-inflammatory drugs (NSAIDS) or steroids. NSAIDs, cox-1 and cox-2 inhibitors are designed to stop pain and inflammation in injury by competitive inhibition with cyclooxygenase activity.[13] NSAIDs produce their analgesic and anti-inflammatory effects by inhibiting cyclooxygenase enzymes critical in the production of prostaglandins and leukotrienes. Inflammation starts when membrane phospholipids (fat layers in the membrane) are converted to arachidonic acid (pro-inflammatory omega 6-like substances).[14] The process continues as arachidonic acid is converted by cyclooxygenases to prostaglandin E2, a hormone responsible for constriction and relaxation of blood vessels. Since cyclooxygenase converts arachidonic acid to growth factors in the body, normal healing is at a disadvantage. By inhibiting new collagen synthesis both NSAIDs and steroids have an adverse effect on bone and soft tissue healing.[15, 16]

NSAIDs cause the acceleration of articular cartilage degeneration in osteoarthritis with side effects to the stomach, GI tract, liver, heart and kidneys. Commonly used NSAIDS are Rimadyl, Deramaxx, Metcam, and Meloxicam. In a normal joint, there is a balance between the continuous process of cartilage matrix degradation and repair.[17] Non-steroidal anti-inflammatory drugs and steroidal drugs disturb this fine balance and accelerate articular cartilage breakdown. Chronic administration of Rimadyl can cause stomach ulcers in dogs, and synthetic prostaglandins often need to be co-administered to prevent this. The Metcam, a popular NSAID, label states that use in cats can cause renal failure and death.[18]

In addition to NSAIDs, many veterinary practitioners frequently prescribe glucocorticoids. Glucocorticoids are a class of potent steroids that interfere with the immune system, thereby decreasing the inflammatory and pain response to respond to acute and chronic musculoskeletal injuries. Commonly used steroids are hydrocortisone, cortisone, prednisolone, methylprednisolone, and dexamethasone. The side effects are numerous and profound: animals become ravenous; increase and redistribute fat, have muscle wasting; behavioral changes that can include aggression; they drink and urinate excessively. Steroids often cause the adrenal glands to stop function and can't be withdrawn abruptly. Steroids can also cause diabetic changes in the body as well as changes in liver function.[19]

Opioids are frequently prescribed for their analgesic effects, especially when either steroids or NSAIDs are insufficient or not well tolerated. Tramadol is a synthetic analog of codeine and commonly used to treat moderate to severe pain. In addition to inducing euphoria, it can cause respiratory depression, inappetence and constipation.[20] As of January 2011, no existing clinical trials for Tramadol demonstrate its effectiveness in the treatment of osteoarthritis for dogs and cats.[21]

Local anesthetics such as procaine, lidocaine, and Xylocaine®, can be used to numb an affected joint or limb, but they can also have systemic effects on the body. These drugs possess the ability to change the function of individual nerves of the autonomic nervous system. A large amount of medical literature documents these physiological changes. Technically, lidocaine stabilizes the cell membrane by stopping the ion flocculation, which is necessary for the conduction of nerve impulses. It causes the sensation of numbness which is normally short acting; two to three hours at the most. Lidocaine is metabolized in the liver. Its half-life, if given intravenously, is typically one and a half to two hours; but if there is compromised liver function it can be longer. When administered to a pet in large amounts there is a chance for lidocaine toxicity.[22] I have seen several animals vomit post-Prolotherapy session but since the drugs are short acting, so is the reaction. Lidocaine may have some long-term effects on the NMDA pain receptors, this reaction is a positive benefit.

Two other classes of drugs have been used off-label for the treatment of pain: Amantadine, an N-Methyl D-Aspartate (NMDA) receptor blocker, is becoming popular for the treatment of chronic pain in veterinary practices around the country. It has been used in human medicine as a Parkinson and antiviral drug. There are also no clinical studies to date on Amantadine. The other new drug used by veterinarians is Gabapentin, an anti-seizure medication, and is known to have some effect on the pain-related behavior response and the exaggerated response to painful stimuli. Gabapentin is a drug being prescribed by veterinarians with no published data.[23]

Injectable and oral polysulfated glycosaminoglycans (PSGAGs) are believed to be chondro-protective and to be supportive of joint homeostasis. Adequan® is a commonly used PSGAG that has been tested and used in animal medicine. It is considered a slow-acting disease-modifying osteoarthritis agent that slows the progression of the disease by modifying bonding to the cartilage.[24] Supplements such as omega-3 fatty acids have also been studied in animals and do help to naturally control the adverse affect of the inflammatory cascade associated with joint pain. Both of these options have minimal negative side effects.[25]

Physical therapy options exist to control and help alleviate pain in both humans and animals. Acupuncture, with or without electric stimulation of the needles, actually raises the endogenous serotonin levels in the body.[26] Serotonin is a feel good hormone but it is short acting and does help in resetting the chronic pain receptors (NMDA). Ultrasound is another modality that is quite effective in enhancing cellular repopulation when used on tendon, ligament and wound injuries in general.[27, 28] Class 3B and Class 4 lasers are becoming commonplace in controlling pain, healing wounds and accelerating repair of injured or arthritic joints, ligaments, tendons and muscle.[29] Magnets with high enough gauss can create fields that can both disorient and control pain receptors in the body.[30] There is also electric stimulation, transcutaneous electrical nerve stimulation (TENS), which is inexpensive and effective in controlling pain and enhancing healing.[31] These options surely have minimal negative side effects and most have been used in human medicine upwards of thirty years.[32, 33]

Exercise is one of the most important means of limiting the pain associated with osteoarthritis, as well as promoting overall natural healing. Exercise raises the body's serotonin (feel good) level and helps to balance the encephalin (pain) response.[34] This being said, how do you get a lame, overweight dog or cat to walk with a knee, back, hip or elbow injury? All of the aforementioned drugs and physical therapy options are usually short-term solutions. When they fail, veterinarians are left with prescribing surgery to try and correct the underlying degenerative joint disease.

Prolotherapy

AN ALTERNATIVE TREATMENT FOR PAIN

Veterinarians have a simple non-invasive, non-surgical option: Prolotherapy. Prolotherapy is a shining light in longer-term pain control, and an alternative solution in repairing hypermobile joints.[35] Prolotherapy helps to alleviate pain from arthritis in humans and we have already established that our pets feel the same pain. Prolotherapy works in humans; therefore, it should be considered a viable solution to pain from osteoarthritis (OA) in animals.[36] In this author's experience, it can sometimes obviate the need for orthopedic surgery. So, Prolotherapy is especially meaningful in older animals.[37]

The results of Prolotherapy are generally predictable and include improved mobility and quality of life of the pet, along with a reduction in, and often the elimination of, pain. After describing how Prolotherapy works, I will compare its use to commonly used surgeries for treating musculoskeletal disorders.

HOW PROLOTHERAPY WORKS

Prolotherapy is performed with natural proliferating and sclerosing agents usually but not always combined with lidocaine or procaine. The solution is injected into the afflicted ligament or tendon where it attaches to the bone. The solution increases the blood supply and flow of nutrients to ligaments and tendons size promoting the healing of tears and decreasing joint laxity. One basic rule of Prolotherapy is that the needle must contact bone before injecting the proliferating solution.[38] Ideally, while injecting, pecking the bone and feeling the periosteum, the vascularized, cellular covering of bone. Just like a microscopic fracture, stimulation of the periosteum osteoblasts and osteoprogenitor cells create and remodel new bone. Co-stimulation of the surrounding stromal cells such as fibroblasts causes them to proliferate and produce collagen. The inflammation or microtrauma of the needle coupled with the insertion of a stimulating substance causes an inflammatory response, and the immune system produces an army of fibroblasts, which synthesize extracellular matrix and collagen. The collagen is needed to thicken, tighten, and strengthen ligaments and tendons.

In his double blind Prolotherapy study conducted in 1982, Y. King Liu, Ph.D. stated that the goal of this therapy is to produce dense fibrous tissue to strengthen the attachments of ligaments, tendons and joint capsules to their fibro-osseous junctions.[39] This study was conducted to assess the influence of a sclerosing (irritating) solution on a rabbit medial collateral ligament (MCL) in situ. The histology lab at the University of Iowa concluded that repeated injections of 5% sodium morrhuate increased the collagen fiber diameters compared to the control group. Both medial collateral ligaments (MCL) and femoral tibial ligaments were studied. The results were that the ligaments had a 40% increase in mass and increase in junction strength of approximately 28%.[40]

In a 1985 study, the effects of sodium morrhuate injections on rabbit patellar tendons and Achilles tendons were analyzed.[41] It was found that the injected tendons were larger in diameter and contained more cells. This sclerosing agent appeared to mimic the early stages of an injury repair sequence.[42] The nine rabbits studied showed a minimum 20% increase in the circumference of both tendons. They were injected three to five times four weeks apart and the control group was injected only one time. The rabbits that were injected more times had a larger number of smaller fibrils, indicating the beginning of tendon thickening and fibrous tissue buildup.

In 1994, the effect of growth factors on the proliferation of fibroblasts was studied. Fibroblasts are a type of cell that synthesizes extracellular matrix and collagen and plays a critical role in wound healing. It was demonstrated that fibroblast proliferation is a basic step in ligament repair. This study actually answered the scientific reason for Prolotherapy efficacy.[43]

WHY PROLOTHERAPY WORKS

Prolotherapy stimulates the normal inflammatory reaction that occurs when ligaments or tendons are injured. The process starts with the initial injury: the micro trauma of a needle and the insertion of the irritating solution. Red blood cells are then released at the site creating an inflammatory phase. Then white blood cells and macrophages (clean-up cells) come to the injured site, attracting fibroblasts. Fibroblasts, the most common cells in connective tissue, secrete collagen proteins needed in healing, creating the matrix linking tissues of the body together. This in turn stimulates other cells to remove the cellular debris from the site.

Once the site has been cleaned up, the ligament repair phase takes place starting at two days and extending up to six weeks. During the repair phase cell reproduction and fibroblast proliferation, ultimately accumulates tropocollagens. Tropocollagens, the next step in the repair phase, is precursor collagen subunits that fill in the injury site. As granulation tissue and collagen continue to repopulate, they reconstruct tendon, ligament and capsule tissue. The remodeling phase lasts three weeks to two years, it culminates with the deposition of new granulation tissue and collagen formation. Remodeling causes a natural tightening of ligaments and tendons. It is thought that maximum tendon and ligament strength is achieved within a year after Prolotherapy has been completed.[44]

George Hackett, MD described Prolotherapy, as the placement of an irritating solution that activates growth factors to provide for the production of new collagen or matrix. Sprains and strains become chronically painful because tensile strength is compromised. The condition is considered connective tissue insufficiency (CTI) and any load on this connective tissue activates pain mechanoreceptors. Prolotherapy provides pain relief via the thickening and tightening of tendons and ligaments. Proliferative therapy is quite safe when used judiciously. The most common complication is pain that lasts two to seven days after the injection session. Dr. Hackett is considered one of the early pioneers of Prolotherapy.[45]

BRIEF HISTORY AND EVOLUTION OF PROLOTHERAPY

Prolotherapy has been used for more than 80 years in the human medical community. It is referred to as "proliferant injection therapy" and "sclerotherapy."[46] Hackett, Earl Gedney D.O., and David Shuman D.O, began injecting ligaments in the 1930s. In 1983, Dr. Y. King Liu in the introduction of his double blind study of rabbit ligaments noted, "Hippocrates reported to have used cauterizing irons to develop auxiliary scar tissue under the human armpit as support for separated shoulder joints."[47] In 2004, Dr. Kent Pomeroy cites a reference to Velpeau who in the year 1835 treated human hernias with injections of iodine. Dr. Pomeroy traced the origins of the first organization for sclerosing methods, which was formed in 1923 and after decades of intra discipline changes and evolution, The American College of Osteopathic Sclerotherapeutic Pain Management (ACOPMS) was granted full status as a college in 1966. The American Association of Orthopedic Medicine (AAOM), which is the Prolotherapy association, is growing and teaching both Prolotherapy and manipulation.[48]

Prolotherapy is used to treat joint hypermobility that occurs when there is inappropriate hinging of a joint. Excessive range of motion creates painful friction from bone on bone contact. Prolotherapy directly addresses the cause of instability and repairs the weakened sites, resulting in permanent stabilization of the joint. When injected into the site of pain or injury, Prolotherapy's inflammatory response fuels the body's formation of new tendon and ligament fibers, resulting in strengthening of the weakened structures. As the joint becomes stronger, pain is relieved via less tension on tendons and ligaments.

Prolotherapy strengthens ligaments and tendons to ensure that joints and bones are appropriately held together to support posture and ambulation. This is true for animals as it is for humans. Joints are weakened when ligaments and tendons are stretched, torn, or fragmented and become hypermobile and painful. Conventional approaches of anti-inflammatory and other pain inhibiting drugs do not help resolve the underlying joint, beyond palliative pharmacological treatment, the surgical approach is thought of, as a chance to cut is a chance to cure. Arthroscopic surgeries can often eliminate an existing nidus of inflammation; they typically do not prevent further joint injury and chronic degeneration due to destabilization. Traditional orthopedic surgeries to stabilize joints often rely on radical resection of bones and rearrangements of joint architecture. Beyond surgery, strategies for managing osteoarthritis should also focus on stabilizing the affected joints to relieve pain and improve the quality of life for the animal.

Prolotherapy has been found to be useful in people for some time and is now being used in animals to treat the following ailments[49]:

- Arthritis or degenerative joint disease (DJD)
- Hip dysplasia and hip laxity and pain
- Anterior cruciate ligament (ACL) injury
- Medial patella luxations
- Neck pain, back pain, spinal stenosis
- Intervertebral disc disease (IVDD)
- Chronic tendonitis
- Elbow dysplasia
- Neck and back pain
- Sprained ankles and wrists
- Partially torn tendons anywhere in the body
- Ligaments and cartilage damage
- Temporomandibular joint (TMJ) dysplasia

I will discuss my findings and compare the use of Prolotherapy to the currently available traditional medical options. I will focus on hip and knee pathology for both dogs and cats. I will also address the topic of the signs of pain and its management through Prolotherapy verses the more traditional pharmacologic options.

USE OF PROLOTHERAPY IN COMPARISON TO SURGICAL TREATMENT OF COMMON CONDITIONS IN ANIMALS

The most common pathologies treated with Prolotherapy by veterinarians are hip dysplasia (HD), knee (ACL) injuries and medial patella luxations (MPL), elbow dysplasia (ED) and back intervertebral disc disease (IVDD). I will focus my attention on the two most prevalent pathologies in veterinary medicine; knees and hips.

According to statistics from 2003, the estimated cost to owners during that year was $1.32 billion for ACL injuries and ruptures.[50] Today it is the most common injury and the primary cause of osteoarthritis in the dog and thus the number one cause of lameness.[51] It is estimated that one in four dogs has had an anterior cruciate repair. Today (2012) it's not known how much is spent in the current market. When performing an Internet search for "ACL in Dogs" there were 2.4 million hits. Searching for "ACL in dogs' surgery costs," there were 1.5 million hits. Judging from the amount of hits these are subjects many pet owners are truly interested in.

Prolotherapy has the ability to rebuild knees and it is an excellent alternative to knee surgery.[52] Combined with the prior rabbit tendon studies, this gives conclusive evidence that Prolotherapy is a viable solution in knee rebuilding for dogs, cats and horses. In 2006, a study was done injecting 24 rats, dextrose injections increased the cross-sectional area of medial collateral ligaments.[53] This study, as well as the previous ones on rabbits, had similar results. Therefore, it can be concluded that Prolotherapy for animals is a viable but little known option.

ANTERIOR CRUCIATE LIGAMENT (ACL) INJURIES

Rupture of the ACL occurs when the tensile strength of the ligament has been exceeded, following acute severe trauma. But it is more commonly damaged because of chronic degenerative weakening. Traumatic ruptures are usually seen in younger animals. Overload on a chronic joint results more from obesity. And there is a higher incidence of ACL in spayed female dogs. The injury typically happens in a large dog between five to eight years, yet in smaller dogs weighing less than 35 pounds occurs later in life. Degenerative joint disease is generally seen bilaterally because 40% to 60% of dogs rupture the opposing leg within 12 to 18 months.[54]

Many of these ACL ruptures may be due to increases in tibial plateau slope (the angle of the knee).[55] This slope is reported to vary between 23 and 25 degrees and is between 13 to 34 degrees in most normal dogs. Conflicting and controversial data is confusing at best. One study of 200 large dogs, concluded that these two values were inversely correlated and the relationship was not strong enough to explain the frequency of ACL rupture in young, large breed dogs by trying to claim poor tibial slopes.

A tibial wedge osteotomy (TWO) is a surgical procedure done to correct the tibial slope as well to stabilize the knee.[56] A TWO is usually done on young, large dogs such as Mastiffs, Labrador Retrievers, and Dogue de Bordeaux. It is hard to ascertain whether or not Prolotherapy could have a positive effect on young dogs with extreme angular deformities of the tibia, but Prolotherapy would and should be included as post operative protocol to strengthen existing tendons and ligaments and aid in managing post operative pain, therefore, expediting rehabilitation.

Several breeds are continually sited as being pre-disposed to ACL rupture, including St. Bernard's, Rottweilers, Labrador Retrievers, Chesapeake Bay Retrievers, Mastiffs, American Stafford Terriers, Akitas and Newfoundland's. When examining these dogs the differential diagnosis should include hip dysplasia.[57] In general, all large and giant breed dogs suffer higher rates of cruciate ligament injury as well as hip dysplasia.[58]

How do we diagnose a full rupture of the ACL verses a partial tear; and what is the significance to the potential outcome of Prolotherapy of the knee?

First physical findings of an ACL injury:

- Gross enlargement of the joint due to fibrosis or scar tissue buildup at the medial aspect of the knee. This is the medial buttress test. Also check for excess warmth.
- Slight clicking sound which may indicate medial meniscus involvement.
- Famous draw sign where the tibia slides forward in regards to the femur.
- Many dogs and cats will sit with the affected limb extended, "Sit Test."[59]

- Accessing the dog or cat's response to full stifle extension.
- Always check for palpable muscle atrophy as you compare both legs.
- Many times there is a visible limp or the dog is walking as it is on its tiptoes on the affected side.

Radiograph findings in ACL:

- Displacement of the proximal tibia relative to the femoral condyles
- Joint effusion with partial obliteration of the infrapatellar fat pad, caudal displacement or cranial displacement of the patellar
- Secondary degenerative joint disease, osteophyte formation[60]

Partial tears of the ACL may involve either the craniomedial band or the cranio lateral band within the knee. They may or may not be associated with gross unsteadiness. Cranial draw signs may not always be present. They are often called stable yet partial tears. If there is instability in flexion of the knee then the term unstable partial tear is used.[61] Dogs with partial ligament tears may experience mild or occasional limping. Early treatment may help to prevent the progression of the partial tear to a complete tear. It may also prevent the strain on the opposite knee, which in a high percentage of cases also has an ACL injury. Most partial tears of the ACL are thought to progress to a complete tear over time if left untreated. Veterinary Prolotherapists claim that partial tears have a better prognosis and are more responsive to regenerative techniques. Conventional veterinarians recommend a Tibial Plateau Leveling Osteotomy (TPLO) for partial tears for dogs and cats over 20 kg's and it is actually becoming the surgery of choice in most knee repair cases. At this time there is no surgical technique for management of the crucient deficient stifle that has been shown to be unequivocally superior.[62]

The two most popular types of common surgical repairs are, first, the tibial plateau leveling osteotomy (TPLO). This procedure rotates the tibial plateau relative to the long axis of the tibia aiming for a tibial plateau angle of six degrees. The bone is cut and stabilized using a plate and screws.[63] Some debate exists regarding a possible increase in implant-associated osteoscarcomas with early designs of bone plate. Any complications for this surgery are more severe than for extra capsular repair technique. This includes fractures, implant loosening, and infections.

Advantages to a TPLO are that it is a precise tibial slope correction with proper surgical technique.[64] It is possible to correct misalignment problems. As pointed out previously there is conflicting research on either side of this issue.[65, 66]

Disadvantages of TPLO are the following:

- Because increased flex of the stifle is created due to the leveling of the tibial plateau, a medial meniscus (the medial meniscus acts as a cushion between the femur and the tibia) release is necessary. The lost integrity of the meniscus is detrimental for joint function and adds to osteoarthritis (OA) progression when associated with meniscal release (partial cutting away of the pad).
- Rehabilitation is slow: the first six weeks are restricted leash walks and that can continue upwards of three months.
- I have seen an unusual number of dogs with stiffened legs unable to bend at the knee after this procedure.

The second most common ACL repair is an extra capsular technique. Ex-Capsular procedures as they are intended provide short-term stifle stabilization, while mature fibrous connective tissue forms to provide long-term stabilization.[67] It is sometimes done by placing a lateral suture, usually with a synthetic nylon leader line. This suture is placed around the lateral fabella to form a bone anchor caudally on the lateral femoral condyle, through a bone tunnel proximally in the tibial tuberosity. This creates a slight protrusion on the outside aspect of the knee. It resembles a "figure 8."[68] This is a quicker and simpler procedure and has been used for 40 years for knee stabilization.

Advantage of extra capsular techniques[69]:

- A simpler and less costly solution to knee stabilization with a stated 80-90% success ratio.
- It is minimally invasive, with low patient morbidity and good long-term outcome.

Disadvantages of extra capsular repair[70]:

- Partial meniscectomy, which may lead to future arthritis.
- Failure to place the lateral tendon suture external to the joint capsule results in excess pain and poor limb function as the suture rubs upon the bone.[71]
- Failure to either anchor the suture properly or place it in the proper isometric position can lead to limited range of motion or premature breakage of the suture material.[72]
- Rehabilitation is slow; sometimes the first ten days to two weeks animal may not bear full weight. Restricted leash walks are necessary. This can continue upwards of three months; no stairs are recommended for at least one month.
- Sometimes muscle atrophy on the surgical leg never resolves.

Statistical data on the risk factors for surgical site infections and infection rates for these surgeries are available. In a retrospective study of 902 canine cases, 6.1% of both surgeries developed infection within six months. In the groups studied, extra-capsular repairs alone had a 4.2% infection rate and TPLO repairs alone had an 8.4% infection rate.[73]

Another retrospective study of 363 dogs examined that complication rates associated with extra-capsular repair of a lateral suture technique was as high as 17.4% of the cases. Of the 17.4% group a majority were heavier and younger dogs.[74]

PROLOTHERAPY INJECTIONS; AN OPTION FOR ACL REPAIR:

Without a doubt, the most compelling nonsurgical option is Prolotherapy.[75] Studies testing Prolotherapy for ACL laxity show short and long term improvement in pain during walking.

- Dextrose and lidocaine are usually benign substances with minimal side effects, however, ACell (Extra cellular matrix), PRP (protein rich plasma or platelets), ozone, fat derived stem cells, and sodium morruhate are all viable solutions. They are all now tested options for inducing cellular repopulation and tendon and ligament repair.[76]
- At least four veterinarians with published case studies for dogs and cats claim 80-90% success rates in correcting ACL tears with Prolotherapy, the same percentage success as any of the above, described surgical procedures. Prolotherapy has a higher success ratio than medial patellar luxation surgery, for which the complication rates alone can run as high as 18%.[77]
- Minimal risk, Prolotherapy is considered non harmful.[78] Prolotherapists are not cutting into bone, cutting out bone (osteotomy) or leaving non-absorbable material, plates or screws under the skin.
- Bruising, swelling at the injection site is minimal; bruising is major in surgery.
- Infection rates reportedly are one in a thousand in Prolotherapy.
- Injection site pain for three to seven days post procedure in Prolotherapy. Many surgeries take months to heal.
- The animals rehabilitate themselves slowly in between Prolotherapy sessions and as the pain goes away and the joints are more stable they actually start to walk on their own with Prolotherapy. Prolotherapy is a progressive buildup therefore rehabilitation is naturally progressive. Prolotherapy does not leave the patient with the long-term sequelae of arthritis; just the opposite. Prolotherapy helps to resolve arthritis. The animals continually improve and muscle atrophies seem to resolve as the animal starts to use the limb or limbs.

HIP DYSPLASIA

It is estimated that 25-30% of all dogs in the United States have hip dysplasia.[79] Hip Dysplasia (HD) is a prevalent, polygenetic, and heritable osteoarthritic disease. It is characterized by laxity of the coxofemoral joint and functional subluxation of the femoral head. As it progresses it causes pain, lameness, and disability.[80] The prevalence of HD in purebred dogs in a typical veterinary hospital population is estimated at 19.7% and the incidence in some breeds is as high as 73% making HD one of the most significant orthopedic traits in dogs. A Cornell study, 51 dogs from 2007-2009, found HD was present in 33 of these dogs (65%).[81] The hip-dysplastic group was composed of nine Labrador Retrievers, nine mixed breeds, five Old English Sheep Dogs, three Golden Retrievers, two Rottweilers, and a terrier. The control group was six Golden Retrievers, five Labrador Retrievers, and two Australian Shepherds, two Old

English Sheepdogs, one Great Dane, one Border Collie and one mixed breed. As previously noted, "Heavier animals had a greater propensity for HD as well as CCL injuries."[82]

Physical findings of hip dysplasia:

- Pain or palpation over the lower pelvic area and the top of the heads of the femurs.
- Crepitus is a finding when slightly moving the top of the femur; usually when hip dysplasia is severe.
- Animals have difficulty getting up and down from a lying position.
- Muscle atrophy in the area of the gluteus muscles.
- Animals walk very stiffly.
- Animals can become apprehensive and sometimes aggressive when stretched or moving hips either laterally (abduction) or distally (forced hip extension).
- Subluxation can actually be felt on palpation, particularly if there is muscle atrophy.
- Reluctance to climb stairs, exercise intolerance, or sitting down frequently during a long walk.
- Bunny hopping is common as the animal is limiting its hip joint range of motion attempting to stop hip pain.

Radiographic findings in Hip Dysplasial[83]:

- Femoral head subluxation or luxation (top of the long bone of the leg movement out of alignment with the hip socket)
- Shallow acetabula (hip sockets)
- Remodeling of the femoral head and neck (arthritis)
- Secondary degenerative joint disease of head, neck, acetabula (arthritis)
- Penn Hip Distraction index high for the breed, this is a measurement of passive hip laxity
- Coverage of at least 50% of the top of the femur, which is the ball of the femur, should fit into the acetabulum; this is the socket on the pelvic bone. When there is less than 50% coverage, the joint is considered dysplastic

There are various techniques for screening young animals for hip dysplasia. One of the most accurate techniques is considered the Penn Hip method, which can predict hip laxity as early as 16 weeks. Dr. Smith, the pioneer of the Penn Hip program, claims that all breeds are affected with hip dysplasia. Hip dysplasia creates major concerns for breeders, veterinarians, and ultimately pet owners. Dr. Smith's advocates controlling hip dysplasia by selective breeding. He believes that this disease is a major animal welfare issue. Unfortunately hip dysplasia is a progressive disease. By the time a definitive diagnosis is made years later it is a bit late to prevent osteoarthritis.[84] By the time the radiographs show signs of secondary osteoarthritis there usually is not any way to correct the bone and joint incongruity.[85] The solutions in traditional veterinary medicine include total hip replacement, femoral head osteotomy, and double and triple pelvic osteotomy. These are all invasive, expensive, risky surgeries.

A WORD ON CONSERVATIVE TREATMENTS

It is thought young dysplastic dogs have a natural tendency to overcome acute pain. This happens in nature with joint capsule remodeling. Conservative management of HD was studied in 1987. A total of 68 dogs were followed for ten years, and it was noted that of 76% of the dogs evaluated, at the end of the study 63% had no pain on forced extension; 79% had normal range of motion; and 72% had normal exercise tolerance. This conservative treatment included controlled exercise, prevention of obesity, use of heat, general exercise and conditioning, balance and proprioception activities.[86] Prolotherapy would be a marvelous adjunct to this conservative treatment, potentially raising the success rates into the 90% range.

Conservative treatments of physical therapy are also inclusive of, weight control, Adequan®, Omega 3 fatty acids,[87] moderate low impact exercise and therapeutic diets. The conventional veterinary community views pharmacology or surgery as a long-term pain reduction solution. The three most popular surgical corrections for HD are total hip replacement, femoral head osteotomy, and also a double and triple pelvic osteotomy. These procedures are anatomy modifying aimed at diminishing disease progression.[88]

Total hip replacement has become thought of as the best surgical option for returning the hip joint to normal function.[89] During the surgery, the top of the femur is

removed and replaced by a ball or acetabular cup implant. Current implants are porous coated and a six-year study revealed an 87% success rate using 50 cases.[90] There is a tunnel bored into the top of the femur for the stem implant to hold. These surgeries are becoming more common place and we do not have the success rates compiled completely, but it is an invasive and expensive surgery ranging between five and ten thousand dollars a hip. The procedure is considered a sophisticated one and application requires specialized training. A 2009 report indicated common complications were luxation (abnormal movement) 4.5%, infection 1.25%, and aseptic loosening 2.25%; although studies indicate 92-95% of canine and feline patients regain excellent function post operatively.[91] The ACVS (American College of Veterinary Surgeons) website recommends 6-8 weeks strict rest followed by 6-8 weeks gradual walk and trot on a leash.[92]

Double and triple pelvic osteotomies are techniques developed to increase the acetabular coverage of the femoral head. Results show osteoarthritis continues but function can be improved.[93] Femoral head osteotomy is the removal of the top of the femoral head; it is considered a salvage procedure. A scar tissue joint is established that has a limited range of motion, a mechanically abnormal gait and muscular atrophy.[94]

HOW PROLOTHERAPY IS USED IN ANIMALS – METHODS

In some instances surgery is unavoidable, however, in today's environment with regenerative medicine techniques available for our animals Prolotherapy needs to be recognized and more widely used. Rehabilitative and regenerative medicine is now mainstream and double blind studies are now confirming their validity.[95] Currently there are many physicians using Prolotherapy with substances such as Protein Rich Platelets (PRP), ozone, testosterone, growth hormone, sodium morrhuate, whole bone marrow or stem cells isolated from bone marrow aspirates, and lipoaspirate-fat derived stem cells. However, the most common solution employed is a combination of hypertonic dextrose and an anesthetic such as lidocaine or procaine.

Prolotherapy normally involves three to five sessions of a series of injections of 50% dextrose and 0.2% lidocaine in equal parts. This is commonly called the Hackett-Hemwall dextrose Prolotherapy method. Normal needle size is 1.5-inch by 22 gauge for hip injections, and 1-inch by 25 gauge in and around the knee. Hip treatments of 5cc are injected at the dorsal and lateral aspect of the hip at four injection sites in and around the articular capsule, surrounding the femoral head of both hips. Knee treatments of 5cc are injected in and around both knees. Injection sites for the knee: lateral tibial collateral ligament, under the infrapatella bursa, into the tendon of the long digital extensor and deeply into the joint space under the patella ligament. Treatments take place approximately three weeks to one month apart. Many times on the last treatment I use ACell®, which is an Extra-Cellular Matrix which acts as an attractant for stem cells in the body.

REGENERATIVE MEDICINE AND PROLOTHERAPY:

Regenerative medicine usually, but not exclusively, implies the use of stem cells. Stem cells and extra cellular matrix (ECM), which recruits new stem cells that are the biologically active mediators of tissue healing. They are capable of differentiating into multiple cell types depending on the molecular signals in their environment.[96] In veterinary medicine, protein rich platelets or plasma are becoming more popular and are viable options. I have found that, in smaller animals, protein rich platelets are difficult because of the amount of plasma that is needed to spin down to get enough platelets to inject multiple sights. Obviously, injecting protein rich plasma itself may not have those limitations. Lipoaspirates (fat obtained from the body) and the spinning them down to re-inject into the patients adds an additional procedure and additional anesthesia, as well as expense, to the protocol. There are currently many companies offering lipoaspirate conversions.

Tissue engineering is a method of regeneration of new tissue. It needs one of three basic elements, stem cells, which could be chondrocytes (progenitor cells), and scaffolds for cell attachment and growth factors. Stem cells are found throughout the body and they can be induced to differentiate into different cell types.[97] This supports the theory that the matrix will recruit cells that can differentiate into site-specific tissue.

There are various companies advocating stem cell use.[98] They function by harvesting fat cells from an animal's body and spinning them down and then re-introducing them to the animal's body. The treatment is used for the

alleviation of pain in arthritic joints. I have found this an expensive and invasive method of pain remediation, usually about two thousand dollars and up, on the other hand, extracellular matrix performs the same role and is not anywhere near the expense.

(ECM) is effective, non-invasive and relatively inexpensive, about eight hundred dollars. Richard Mitchell, DVM, reported treating 190 suspensory ligaments and superficial and deep flexor tendons lesions in horses from 2002 through 2005. He concluded that, "Encouraging results called for further investigation." Dr. Mitchell has stated that, "The commercial availability of products that do not require harvesting and ex vivo expansion, would be advantageous to practitioners."[99] He worked with the product manufactured by ACell®. Extra-cellular matrix (ECM) consists of a complex mixture of structural and functional proteins. It has been used as a bio scaffold for the reconstruction of many different tissue types. The ECM response induced remodeling is a different phenomenon from that of scar tissue formation.[100]

In combination with Prolotherapy, dextrose and lidocaine to thicken the ligaments either around the hip or the knee, ACell injections, given in the same way as Prolotherapy injections, act to regenerate knee tissues such as ACLs, medial menisci and in and around the coxofemoral joint (hip joint). In a double blind study of 20 dogs between the ages of three and 14 years with hip osteoarthritis (OA), treatment with ACell injections improved the treated dogs within seven days and continually improved their condition over a six-month period.[101] Its antimicrobial activity is also a benefit from the standpoint of practitioner confidence.[102]

EMERGING ROLE AND LIMITATIONS OF PROLOTHERAPY IN VETERINARY MEDICINE?

There is currently a resurgence of interest in Prolotherapy for both humans and animals. As people search for alternatives to surgeries, such as total hip and knee replacement for themselves they do so for their pets as well. There have been numerous articles published on the subject of animal Prolotherapy.[103] There is a short report from Roger Dehaan, DVM, who has been practicing Prolotherapy on animals for over 20 years.[104] He spoke of Prolotherapy as "a silver bullet" in regard to treating connective tissue and ligament reconstruction and regeneration for our pet population.[105] The February 2010 issue of *The Whole Dog Journal* described Prolotherapy as a "conservative management and an option for ligament injuries."[106] An article published by *Dog Fancy's Natural Dog* Winter 2011 focused on the merits of Prolotherapy and interviewed an owner of a pair of Newfoundland's that had benefited greatly from the treatments.[107] Case studies have been published in the *Journal of Prolotherapy* in six issues since August 2009.[108-113] All participating practitioners have experienced the same 80-90% success rates with animals returning to normal function.[114-119] This leaves a 10% to 20% failure rate.[120]

The following are possible causes for the 10% to 20% failure rate:

- Not following the prescribed treatment format.
  - A minimum of three to five treatments may be necessary to obtain adequate tendon strength.
  - The specified time frames for treatment must be adhered to.
- The solution is too weak. The dextrose percent too low or sodium morrhuate less than 5%.
- The points treated are not the source of the pain or there is a compensating lameness that has not been previously addressed.
- The patient is taking anti-inflammatory medication. Stopping the inflammatory reactions stops the very response needed to elicit proper Prolotherapy response.
- Rehabilitation is inadequate and the dog is let off a leash too quickly
- Jumps and plays too early, creating a new injury.
- The older the dog or cat, the higher the failure rate. A rule of thumb is that 8 to 12 year old dogs and 12 to 15 year old cats have a lower success ratio.
- Immune compromised animals may not respond well.

Conclusion

With all the alternatives now available in veterinary medicine and a large body of evidence that Prolotherapy works, the question shouldn't be, "Why Prolotherapy?" But, "Why not Prolotherapy; why not regenerative medicine?" Regenerative medicine is the medicine of the future. We have years of scientific studies on rabbits

and rats and actual repeatable data for the strengthening and regrowth of tendons and ligaments. There are currently veterinarians practicing Prolotherapy and getting excellent results. Prolotherapy as a modality is a viable non-surgical option for alleviating animal pain and helping to heal soft tissue injuries. ■

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