A Whole New World: Newer modalities and therapies for osteoarthritis and soft tissue injuries

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Extracorporeal Shockwave Therapy (ESWT)

Principles of Shockwave Therapy

Extracorporeal shockwaves are sound waves of high pressure and velocity produced outside of the body. Traditionally they have been primarily used in lithotripsy for dissolution of kidney stones and gallstones. They have specific physical characteristics, including nonlinearity, high peak pressure followed by low tensile amplitude, short rise time, and short duration (10 ms). These pressure waves differ from ultrasound waves because of their lower frequency, minimal tissue absorption, and lack of a thermal effect. In comparison to ultrasound waves, the shockwave peak pressure is approximately 1000 times greater than the peak pressure of an ultrasound wave. Delivery of energy to tissue requires the use of ultrasound gel in conjunction with a percussive handheld applicator. Energy can be focused via spherical arrangement of crystals, spherical generator, or acoustic lenses. Focusing energy results in greater tissue depth penetration, up to 110 cm, with a rapid decline of energy at the periphery, allowing an intense amount of energy delivery to a relatively small area (approximately 80% of the maximum shockwave pressure).

There are three primary methods through with shockwaves are produced: electrohydraulic, electromagnetic, and piezoelectric. An alternative to focused extracorporeal shockwaves exists as a radial shockwave device, or a ballistic generator. Commonly used devices in veterinary medicine are electrohydraulic, piezoelectric, and radial.

Electrohydraulic shockwaves are created by utilizing a high-voltage spark gap, causing plasma bubble generation. Expansion of the bubble results in sonic pulse propagation and subsequent collapse results in a reverse pulse, manifesting a shockwave. Electrohydraulic generators produce the largest focal volumes with lower energy flux density and overall high energy transfer. These devices may require sedation for treatment due to some discomfort during therapy and noise from the device, however fewer treatment sessions are usually needed to see an effect. Most existing veterinary research has been utilizing this shockwave method. Recently newer advances in technology with this device have produced an application probe (also called a trode) that does not require sedation for most patients and research is underway to determine its efficacy.

Piezoelectric generators use many crystals (>1000), mounted in a sphere, that expand and deform when stimulated by high-voltage electricity, initiating a pressure wave. The arrangement of the crystals results in a small, defined focal volume and high-energy flux values and low overall energy transfer. These devices do not generally require sedation, are well tolerated, but may need more frequent treatments.

Radial or ballistic shockwave therapy differs from extracorporeal shockwave therapy in how waves are propagated and the depth of penetration for treatment. Shockwaves from this device are generated pneumatically (mechanical concussion) and are propagated through tissues in a radial

pattern. Radial pressure waves have lower energies, characterized by a slower rise time. Energy produced by this method is greatest at the applicator-skin interface and rapidly decreases in deeper tissues. This applies energy to a wider circumference with decreased tissue penetration and is best used for more superficially located conditions.

Biologic Effects

The mechanism of shockwave therapy is not fully understood. The primary effects of shockwaves are produced by the generation of mechanical forces. Secondary effects occur by indirect generation of mechanical forces through cavitation. Compression and tension generation occurs as the shockwave travels through the tissue. Varying amounts of reflection and transmission of energy occur at varying interfaces. Cavitation bubbles are made during the tensile phase of the shockwave, and as size increases, a large amount of energy is delivered to the bubble. Cavitation at the surface interface is the mechanism by which fragmentation of uroliths occurs. Cavitation also leads to the production and release of free radicals creating chemical reactions within the tissue. An increase in cellular permeability may also occur with ESWT.

Several of the proposed mechanisms of action for ESWT include the following: Increased expression of cytokines and growth factors, decreased expression of high levels of inflammatory mediators, increased circulation and promotion of neovascularization, stimulate proliferation of tenocytes and osteoprogenitor differentiation. The mechanism of action for induction of analgesia is poorly understood however some theories include 1) Hyperstimulation of nociceptors resulting in an increased input to the periaqueductal gray area which in turn promotes descending inhibition. 2) Induction of cell damage and destruction of unmyelinated sensory fibers from shockwave application prevents appropriate membrane potentials required for transmission of signals. 3) Reduction of substance P and reduced synthesis of substance P in dorsal root ganglia and 4) Production of nitric oxide which plays a role in suppressing the inflammatory process, vasodilation, and angiogenesis.

Uses/Indications/Precautions

The most common indications for use of shockwave therapy in veterinary medicine are tendon and ligament injuries, adjunctive therapy for osteoarthritis, delayed/non-union fractures, lumbosacral disease, and non-healing/chronic wounds (potential antibacterial properties). Current studies support use for chronic tendinopathies, post-operative TPLO, bone healing, and osteoarthritis.

Some considerations for use are the requirement to shave for therapy, possible need for sedation, cost of treatment (varies by unit), and frequency of treatment. Side effects can include mild post-treatment discomfort, bruising or petechiation. Precautions/contraindications are neoplasia, open growth plates, application over major nerves/vessels, osteomyelitis, immune-mediated joint disease, discospondylitis, infectious arthritis, unstable fractures, or patients with neurologic deficits.

Pulsed Electromagetic Field Therapy (PEMF)

PEMFs have been used for a variety of purposes, but their main therapeutic purpose is for enhancement of bone or tissue healing and pain control. These devices were first introduced in the late 1970s and approved for use by the FDA as bone-growth stimulators. Electromagnetic waves activate a

variety of signaling pathways to reduce inflammation, increase blood flow, and facilitate healing. These are considered non-thermal, non-invasive, non-pharmaceutical anti-inflammatory devices (NPAID).

Faraday's law of induction states that a time varying (pulsed) electromagnetic field will induce an electrical field (or electromotive force) in a conductor (like tissue). Differences in waveforms influence the electric field stimulated in tissues and each company has their own proprietary transmitter. Electromagnetism is generated by running an electric current through a coiled wire (electromagnetic induction). These devices can be placed over the tissue/region including over wraps and blankets. PEMFs are hypothesized to have electric rather than magnetic effects on tissue. PEMF stimulation increases nitric oxide by the calcium-calmodulin signaling pathway. The calcium binding step is voltage dependent and PEMF induces this pathway. CaM binding activates endothelial nitric oxide which increases/activates cyclic GMP. Effects of this cascade include vasodilation and increased circulation, decreased inflammation (via a reduction of pro-inflammatory cytokines) and increased angiogenesis (including the growth factors VEGF and FGF-2). Other secondary effects that have been seen include an increase in heat shock proteins which can have cytoprotective and anti-apoptotic effects, increased expression of adenosine receptors in a variety of cells/tissues (reduces prostaglandins and inflammatory cytokines), and increased expression of bone morphogenetic proteins which play a role in bone and cartilage formation.

Devices and Uses

There are a variety of PEMF devices available for humans as well as in the veterinary field. Some of these devices produce a more targeted signal allowing for shorter treatment times. These devices come in various forms including loops, beds, wraps, boots, blankets, paddles, pads, and mats. The most common uses include post-operative pain and healing, intervertebral disc disease, osteoarthritis, soft tissue injuries, wounds, and slow healing fractures. Newer uses include anxiety and oral/dental pain. Treatments can be performed as often as every 2 hours if needed, and devices are portable allowing for owners to use at home.

There have been very few side effects or contraindications listed for PEMF. The primary precaution for use is around a pacemaker (at least 6 inches or more away) and caution using close to a hemangiosarcoma. PEMF use is not contraindicated in most types of cancer sites and has been used in peer-reviewed human clinical trials on patients undergoing reconstructive surgery post-cancer with no adverse effects of any kind.

Regenerative Medicine

Regenerative medicine is a continuously evolving branch of medicine that focuses on the use of biologics to grow, repair or replace damaged or diseased cells, organs, or tissues. In veterinary medicine the most used forms of regenerative medicine are platelet rich plasma and mesenchymal stem cells, although other methods being used including autologous conditioned serum and autologous protein solution.

Platelet Rich Plasma (PRP)

Platelet rich plasma can be technically defined as plasma in which the platelet count exceeds that of whole blood. It is generally accepted that PRP should be low in red blood cells. The role of leukocytes in PRP is controversial and you will find references to both leukocyte rich and leukocyte poor

preparations. Neutrophils can potentially exacerbate a disease or condition through the release of inflammatory cytokines, reactive oxygen species, and matrix metalloproteinases. However, WBC's increase the concentration of growth factors in PRP which can be beneficial. Another current unknown, is the ideal viable platelet concentration for a PRP sample. Based on human studies it has been proposed that platelet concentration should be 3-5 times baseline platelets. These factors are also confounded by the fact that each commercial machine for PRP processing have been shown to all have varying levels of platelets and WBCs.

The therapeutic effect of PRP is primarily attributed to the degranulation of the platelets' alpha-granules. These alpha-granules store a variety of growth factors and cytokines, including platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), transforming growth factor-beta (TGF-β1), fibroblast growth factor (FGF), and platelet-derived epidermal growth factor. These growth factors and cytokines can help reduce inflammation, protect intact and newly formed tissue, recruit pre-regenerative cells (such as mesenchymal stem cells and macrophages) and support neovascularization. For the optimum effect, the platelets must be activated to help facilitate the release of growth factors into the environment. In vivo, this can be accomplished by contact/interaction with collagen at the location of injection. Many other activators have been investigated such as soluble collagen, calcium-based products, and thrombin, all of which have been shown to increase platelet activation and growth factor release compared to no activation.

Mesenchymal Stem Cells (MSC)

The primary type of stem cells used in veterinary medicine are mesenchymal stem cells. MSCs are undifferentiated cells that have unique characteristics such as the ability to move during angiogenesis, differentiate into specialized cell types (osteoblasts, adipocytes, or chondroblasts), proliferate and regenerate, and release immune regulators and growth factors.

Initially, MSCs were thought to regenerate tissue via engraftment and differentiation. However, it has been found the MSC survival at in the target tissue, following transplantation, may be negligible. Growing evidence suggests that MSCs exert their therapeutic effect predominantly by secreting bioactive factors (the "secretome") that modulate the immune response, reduce inflammation, inhibit cell death and induce and stimulate endogenous regeneration. Additionally, perivascular localization of MSC in various tissues plays an essential role in enabling these cells to detect local or distant tissue damage and respond to it by directed migration to the site of injury and participation in the healing process.

Sources of MSCs include fetal tissue such as umbilical cord and blood and adult tissues such as bone marrow, skin, adipose tissue, synovium, periosteum, and dental pulp. The most studied and widely used sources of MSCs in human and veterinary medicine are bone marrow and adipose tissue. These can be either collected from the patient (autologous) or a donor (allogenic), although due to concerns of immunogenicity, the autologous route is primarily used. Bone marrow use allows for same day administration but fewer MSCs are obtained unless cultured and expanded. Adipose tissue has also proven to be a readily available source of MSCs after culture and expansion and some studies have found higher isolation success and proliferation rates found with adipose tissue versus bone marrow. The most recommended region for collection of adipose tissue is the falciform ligament.

Uses for Regenerative Medicine

There have been numerous proposed uses for regenerative medicine including musculoskeletal conditions (especially tendon and ligament injuries), osteoarthritis, skin disease and wounds, renal disease, GI disease, liver disease, neurological disorders, ocular disorders, cardiac, and reproductive system diseases. Of these, the most common uses are tendon and ligament injuries and osteoarthritis. Despite current advancements in regenerative medicine, there is still much work to be done and many questions to be answered.

Monoclonal Ab Therapy

Introduction

In the past several years, there has been growing interest and research in the use of monoclonal antibodies for everything from allergies (Cytopoint®), COVID therapy, and now osteoarthritis. Two products have been approved for use to treat osteoarthritis in Europe. The canine version is bedinvetmab (Librela®) and the feline product is frunevetmab (Solensia®). Just this year, Zoetis announced the FDA approval of Solensia® in the United States and it should be available for use later this year. Both of these products are specific monoclonal antibodies that specifically target nerve growth factor.

There is increasing interest in addressing the role of cytokines, chemokines and neutrotropins in joint pathology and pain. Activation and sensitization of peripheral nociceptors by cytokines is one of the main peripheral mechanism for joint pain. Monoclonal antibodies (mABs) can specifically bind to target molecules (cytokines, receptors or cells) and this binding results in blocking activity of the target. These mAbs are produced by single B-lymphocyte clones in mice or via recombinant engineering. Mouse engineering technology lowers risk of immune reactions (immunogenicity) which are undesirable as they can neutralize the action of the therapeutic mAbs and hypersensitivity can result in morbidity & mortality.

Nerve growth factor (NGF) is one of the cytokines that has received significant attention as a key regulator involved in both inflammatory and neuropathic pain. In early growth it is critical in the development and maintenance of sensory and sympathetic neurons. In adults it modulates nociceptive neuronal activity. It is produced and released by peripheral tissues in response to injury, disease, & noxious stimuli. The activity of NGF is primarily mediated by binding to tropomyosin receptor kinase A (TrkA). This causes increased sensitivity of the sensory neuron & changes in phenotype of the neuron and increased expression of pronociceptive neurotransmitters. NGF binds to TrkA on inflammatory cells causing further release of inflammatory mediators (histamine, serotonin and more NGF). This can lead to peripheral sensitization, neurogenic inflammation, and cell-mediated inflammation.

Recent Studies and Use

Both bedinvetmab and frunevetmab have undergone safety, immunogenicity, pharmacological, and efficacy studies. They are intended to be once monthly subcutaneous injections for the treatment of osteoarthritis. In clinical trials for efficacy, decreased pain scores, improved client outcome scores, improved global health assessments, improved veterinary assessments, and increased activity was noted.

In feline safety studies, no significant blood parameter changes were seen with use and it has been deemed safe to use in IRIS stage I and II cats. There were some increased dermal reactions (in

both treatment and placebo groups) and mild increases in renal disease (but also in both groups). Use concurrently with NSAIDs has not been studied in cats.

In canine safety studies, there were no increased incidents of adverse effects compared to a placebo. In healthy dogs, bedinvetmab was safely used concurrently for 14 days with NSAIDs but no current studies have been undertaken to determine if it can be used long term in conjunction with NSAIDs. In efficacy studies, patients were not allowed to be on concurrent NSAIDs or steroids.

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