Update on Shockwave Therapy

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Objectives:

- Know that a shockwave is a pressure wave with specific characteristics.
- Understand the basics of how a pressure wave can stimulate anabolic processes within cells.
- Recognize the applications of shockwaves that could benefit your patients.
- Know how shockwave therapy can be used in conjunction with other treatment modalities.

Introduction:

Initially human patients suffering from hip osteoarthritis (OA) and simultaneously undergoing urolithiasis lithotripsy treatment noted significant improvements in pain following treatment, leading practitioners to believe that energy from the shock wave may have positive physiologic effects on musculoskeletal conditions. Ultimately, when it was established that shock waves increased radiographic bone density of the pelvis following lithotripsy,[1] shock wave therapy began to be formally used for orthopedic conditions to stimulate tissue and bone formation.[2] The first subsequent musculoskeletal application of ESWT was for healing nonunion long bone fractures.[3]

A true shock wave for medical purpose has been defined as an acoustic pressure wave characterized by alternating amplitudes of high, rapid (within 1/billionth of a second) positive pressure (ten to a hundred) megapascals (MPA) followed by weaker, tensile oscillations of negative pressure several microseconds later. For perspective, 10 MPA is 100 times atmospheric pressure. The high peak pressures and subsequent negative pressure wave is the hallmark of a true shock wave.[4]

Over the past three decades, extracorporeal shock wave therapy (ESWT) as a treatment modality for equine orthopedic disorders has sparked exponential interest among practitioners. Equine orthopedic applications include a variety of conditions including osteoarthritis,[5] thoracolumbar pain,[6] navicular syndrome,[7] tendinopathy[8] and proximal suspensory desmopathy.[9] Despite veterinary use for decades, ESWT's clinical applications are quickly evolving.

Mechanisms of Action of Extracorporeal Shock Wave Therapy

High energy pressure waves' (shock waves) primary physical effect is believed to be via mechanotransduction and beneficial effects in downstream cytokine signaling. Mechanotransduction describes the cellular processes that translate mechanical stimuli into biochemical signals, enabling cells to adapt to their environment.[10] The initiation of the signaling pathways results in the ultimate biologic outcomes seen with shock wave therapy including control of inflammation, angiogenesis, and stimulation of cytokine production. Early ESWT studies in murine and human models found increases in expression of favorable cytokines associated with improved healing responses (specifically transforming growth factor beta (TGF-β1) and vascular endothelial growth factor-A (VEGF-A).[11] Studies in horses have also noted the upregulation of beneficial anabolic cytokines following ESWT.

There are numerous biologic components that can act as mechanosensors including stretch activation of ion channels, compression of intercellular space stimulating paracrine signaling and direct cell nuclear changes from intracellular deformation, among others. As previously discussed, shock waves have high peak pressures and ultimately negative pressure resulting in a wide range of compression, tension and shear forces that can all initiate mechanostransduction. The initiation of the signaling pathways results in the ultimate biologic outcomes seen with shock wave therapy including control of inflammation, angiogenesis, and stimulation of cytokine production.

Early studies found increases in expression of cytokines associated with improved healing responses (specifically TGF-β1 and VEGF-A) in a segmental defect model of rats following 500 pulses of ESWT with an energy flux density (EFD) of 0.16 mJ/mm^2.[11] Similarly, the same research group appreciated increased expression of TGF-β1 and insulin-like growth factor-1 (IGF-I) in both the acute and later stages of healing when an experimental Achilles tendinopathy model was exposed to the same shock wave parameters.[12] Studies in horses have also noted the upregulation of anabolic cytokines following ESWT. In a collagenase model of proximal suspensory desmitis, ESWT treatment with a total of 1500 pulses at 0.15 mJ/mm^2 applied at weekly intervals for a total of three treatments resulted in greater expression of TGF-β1 four weeks after the last ESWT treatment compared to the untreated contralateral limb. In a wound model in horses that were treated with a lower EFD (0.11 mJ/mm2), there was no increase in TGF-β1 and only an increase in IGF-1 from 28 days onward.[13] The lack of increased TGF-β1 could be that the macrophages in the wound model were already stimulated or that the shock wave therapy used was not appropriate to stimulate the TGF-β1 production. Findings like this may ultimately be explained with further mechanistic investigations of altered cytokine production following exposure to ESWT.

Toll-like receptor 3 (TLR3) is a component of innate immunity and when activated plays a role in inflammation and subsequent angiogenesis. A mediated angiogenic response via TLR3 pathways following ESWT has been identified.[14] Specifically, a rat hind limb ischemia model (via femoral artery ligation) demonstrated nearly normal limb perfusion in wild type mice after 28 days following ESWT exposure. This was in contrast to TLR3-knockout mice for which minimal limb reperfusion was noted, further indicating the significance of TLR3 in the repair and reperfusion process. Another investigation into the cellular mechanism focused on how shock wave therapy affects reactive oxygen species and induction of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) pathway to exert a potent, downstream chondroprotective effect.[15] Notably, it was determined that shock wave increased extracellular matrix synthesis without affecting cell viability. As mechanistic insight is gained, further investigation into specific shock wave therapy details like EFD, pulse number, and waveform can be evaluated to maximize the desired outcomes and incorporate into clinical use.

Clinical Applications

Proximal Suspensory Desmopathy:

One of the most common clinical applications of ESWT is for the treatment of both forelimb and hindlimb proximal suspensory desmopathy.[16-19] The first report of electrohydraulic ESWT to treat proximal suspensory desmopathy was reported by Lischer et al in 2006 for which 34 forelimb and 22 hindlimb cases were enrolled and followed for one year after diagnosis.[17] Authors utilized 2000 pulses at an EFD of 0.15mJ/mm^2 every three weeks for a total of three

treatments (Equitron[a]) in addition to stall rest and a 3-month controlled exercise program. Nearly 62% of forelimb PSL desmopathy cases had returned to full work by six months, and roughly 56% were still in full work one year after diagnosis. In contrast, only roughly 41% of hindlimb PSL cases had returned to full work by 6 months, which decreased to 18% one year after diagnosis, highlighting the frustrating reoccurrence of hindlimb PSL desmopathy.[17]

When the rate of return to athletic function in 75 sport horses with hindlimb PSL desmopathy treated either surgically, with a series of three ESWT sessions or with a combination of the two modalities was investigated, horses treated with ESWT returned to their previous level significantly sooner.[16] Specifically, 41 horses underwent surgery with 24 returning to their previous level of work at an average of 10.1 months. This was in comparison to 34 horses that received ESWT with 20 returning to their previous level of work at an average of 7 months.

When 100 western performance horses diagnosed with forelimb or hindlimb proximal suspensory desmopathy were treated with either ESWT or platelet rich plasma (PRP) therapy in a prospective randomized clinical trial, ESWT treatment was associated with going back to work 3.8 times more likely at one year compared to PRP, regardless of baseline ultrasound severity.[9] Interestingly, horses treated with ESWT demonstrated greater lameness improvement compared to PRP at 4 days post treatment, but at one year, horses with more severe ultrasound changes responded better to PRP. Authors concluded that both PRP and ESWT can be expected to yield favorable therapeutic responses in western performance horses, but baseline ultrasound severity assessment may help guide treatment selection .

In a recent review of the application and efficacy of ESWT in equine tendon and ligament injuries, authors noted differences in ESWT energy settings, pulses delivered, concurrent therapies and treatment intervals between the above-described studies, highlighting the need for standardized clinical trials for a more direct comparison of treatment-specific effects across a variety of injuries.[19] As clinical use often supersedes academic research, specific, evidence-based protocol recommendations are still lacking, but would be beneficial to the practicing clinician. In a subsequent meta-analysis evaluating return to function rates in horses with PSL desmopathy treated with ESWT compared to conservative/surgical management, authors were unable to definitively conclude whether ESWT therapy improved return to function rates due to differences in study design, outcome measures and the retrospective nature of published reports, but they did state that no published reports indicated a worse functional outcome following ESWT. [20]

The application of ESWT moved from bone to tendons and ligaments as a result of early studies at the enthesis interface. A study that initially highlighted these findings delivered 1000 pulses at 0.18 mJ/mm^2 to the Achilles insertion in 8 dogs.[21] The ESWT-exposed sites demonstrated significantly more neovascularization than those not receiving ESWT.

In horses there are two studies that have evaluated the effects of ESWT on collagenase-induced SDF tendonitis.[22,23] Both studies utilized collagenase-induced lesions in the SDF tendon at the mid- metacarpal region and were very similar in outcome. Ultrasonographically, the treated and control groups were similar throughout the study periods. Histologically, the treated tendons had a more normal histologic appearance, suggesting that healing was occurring at a faster rate in the ESWT-treated tendons. Specifically, the ESWT-treated tendons demonstrated more parallel collagen fibers in one study,[23] while a clear and significant increase in neovascularization of the treated tendon was appreciated in the other study.[22] Unfortunately,

neither of these studies evaluated the biomechanical strength of the repaired tendons. Similar to superficial digital flexor tendons, two studies have evaluated the ultrasonographic healing of suspensory ligaments following collagenase-induction of lesions.[24,25] In both studies, the ultrasonographic measurements demonstrated improved lesional healing in the ESWT-treated groups. Caminoto *et al* demonstrated increased expression of TGF-β1 in treated ligaments while McClure *et al* found a greater amount of proteoglycan deposition within the collagen matrix.

Navicular Disease:

When the clinical effectiveness of ESWT for treatment of navicular syndrome in 27 horses was evaluated, lameness was decreased in 81% of horses evaluated by an unblinded evaluator and in 56% of horses evaluated by blinded evaluators.[7] Navicular bone ESWT was performed using an electrohydraulic system (Orthowave[b]) while the horses were under general anesthesia in lateral recumbency . Fluoroscopic guidance was used to focus the ESWT at the appropriate location for a total of 2000 pulses (1000 pulses through the frog and 1000 pulses through the heel at 0.89 mJ/mm^2 . The treatment protocol and positioning was based on the shock wave generator being utilized. Following treatment, horses were stall rested for one week then limited to hand walking and ground-work for an additional 5 weeks before resuming full work. Follow-up examinations were performed 6 months following treatment in absence of any further treatments for navicular syndrome. While imperfect in study design, authors concluded that ESWT represented a viable, non-invasive mechanism to treat navicular syndrome diagnosed clinically and radiographically in horses.

In the authors' opinion, current clinical usage of ESWT for management of pain from the navicular apparatus has evolved more towards managing acute navicular bursitis and associated soft tissue pathologic change associated with the navicular bone, for which MRI has significantly enhanced lesion characterization. Additionally, modern ESWT generators have improved subjective clinical responses due to the ability to deliver higher EFD than original portable units.

Distal Tarsal Osteoarthritis:

Distal tarsal osteoarthritis (OA), partial to complete ankylosis and the spectrum of pathologic changes in between still represents a unique challenge for sports medicine clinicians in the actively competing equine athlete. Indications, techniques and anecdotal clinical experiences using ESWT for the treatment of OA in the horse have been previously described.[26] When the effectiveness of ESWT for the treatment of bone spavin in 74 horses was evaluated, application of 2000 pulses at 0.89 mJ/mm^2 to the affected joints decreased lameness grade by at least 1 in 80% of the horses.[27] Horses were diagnosed with bone spavin by lameness evaluation, flexion tests, diagnostic anesthesia and radiographs or fluoroscopy, and follow-up examination and radiographs were obtained 90 days post-treatment. Following treatment, all horses were stall-rested for 1 week, then limited to hand walking and ground-work for an additional 4 weeks before resuming full work. Interestingly, follow-up radiographs demonstrated no consistent changes when compared to pre-treatment, but horses with osteophyte formation along the dorsal or dorsomedial aspect of the tarsometatarsal (TMT) joint seemed to improve most consistently. The mechanism associated with this reported decrease in lameness is unknown, but discussed potential mechanisms included strengthening of the subchondral bone or facilitated ankylosis that was not appreciable radiographically.

Thoracolumbar Pain:

Two anecdotally reported ESWT guidelines for spinous process impingement (SPI) and dorsal articular process (DAP) OA have been published.[28,29] McClure *et al* utilized 50 pulses at an energy setting of 0.15mJ/mm^2 with a 35 or 80mm probe on the left and right sides every 1 cm for the length of spinous process sclerosis.[29] Allen *et al* described applying 1000-2000 pulses with a 35mm probe axially and abaxially over the entire length of the thoracolumbar spinous processes for SPI, in contrast to the same pulse numbers applied abaxially over the left and right sides of the vertebral column with the 80mm probe for DAP.[28] These sessions were then followed by 2 days of athletic rest, then 3-5 days of gradually returning to exercise A recent non-randomized clinical trial by Trager *et al* utilized 1500 pulses with an 80mm probe at a power setting of E4 (113 mm penetration depth) and energy flux density of 0.13 mJ/mm^2 to document improvements in mechanical nociceptive threshold (objective assessment of pain) in 12 horses with back pain over a 56-day study period.[6] The generator was oriented adjacent to midline and angled approximately 45 degrees towards the spine during all ESWT application sessions on study days 0, 14 and 28. Authors also investigated multifidus muscle cross sectional area for which no significant changes were appreciated, concluding that ESWT appears to offer pain modulation in the clinical management of back pain.[6]

Effects on Wound Healing:

Several studies performed on human, rat and swine wounds have described beneficial effects of ESWT including increased rate of epithelialization and stimulated healing of skin flaps, similar to that seen with gene therapy.[30-32] The expression of growth factors, increased rates of healing in multiple tissues and the demand for nonpharmacologic mechanisms to assist in healing of diabetic ulcers and other wounds led to the evaluation of ESWT for wound healing. In a study evaluating repair of partial thickness wounds in pigs, researchers found that the effect of ESWT on the rate of epithelialization was dose related.[30] Survival of epigastric skin flaps in rats has also been shown to be enhanced by the application of ESWT.[31] ESWT stimulated healing of skin flaps equivalent to that of exposure to gene therapy with TGF-β1 or VEGF. These data have transferred to research in humans where the increased rate of re-epithelialization in human patients with deep partial-thickness burns has been an ongoing source of investigation.[32] In a multicenter randomized, blinded and controlled study, ESWT was found to be an effective therapeutic modality in combination with standard care for neuropathic diabetic foot ulcers in humans that did not respond to standard care alone.[33]

Results on the effect of wound healing in horses specifically are mixed. Surgically created wounds on the dorsal metacarpus treated with a wide focus electrohydraulic shock wave generator designed for wound therapy did not heal faster than untreated controls,[34] although they did appear to have less inflammation and less exuberant granulation tissue than the untreated controls. In contrast, adult horses with surgically created full-thickness metacarpal/metatarsal wounds that included underlying periosteum demonstrated significantly shorter healing time when treated with ESWT (mean 76 days) in comparison to those that were not ESWT-treated (mean 90 days).[35] Interestingly, bacterial culture, area of epithelialization, percentage of wound contracture and staining intensity of growth factors did not differ between ESWT-treated and untreated wounds, leaving authors to conclude that although ESWT may have stimulated healing of wounds, the exact mechanism by which healing was stimulated could not be identified. In horses with surgically created skin wounds in the cervical region treated with the same wide focus ESWT generator, the expression of TGF-β1 was decreased throughout the wound healing

period and IGF-1 was significantly increased at 28 days.[13] It was hypothesized that the decrease in TGF-β1 may decrease exuberant granulation tissue. Lastly, a single case report that utilized ESWT for adjunct treatment of an extensive burn injury over the dorsum of a horse documented no adverse effects and a decrease in pruritis.[36]

Extracorporeal Shock Wave Therapy & Biologics:

With the increasing use of biologic therapies in the treatment of equine orthopedic injury, there is persistent interest in the interplay between ESWT and regenerative medicine options. From an *in-vitro* perspective, when adipose-derived stem cells (ASCs) were treated with different pulses of focused ESWT, treated cells showed increased proliferation and expression of kinases involved in cell growth and differentiation, and increased expression of cytoskeleton proteins[37] leading authors to conclude that ex vivo pre-conditioning of equine ASCs with ESWT application followed by re-implantation into tissue lesions may help improve their efficacy. Specifically, three treatment groups were utilized according to standard means of delivery in equine clinical use: 1) control group receiving no ESWT; 2) Group 1 that received 9 rounds of 1000 pulses; 3) Group 2 that received 3 rounds of 2000 pulses. Significantly higher amounts of cell apoptosis was appreciated in the 2000 pulses group while phosphorylation of Erk1/2 was significantly higher in the 1000 pulses group potentially indicating the importance of dose selection.

When authors investigated if application of shock waves either with a "standard" (2cm focal width and medium energy density) or a "power" (1cm focal width and higher energy density) probe to PRP samples increased the concentration of TGF-B and platelet-derived growth factor BB (PDGF-BB), authors noted 46 and 33% significant increases in TGF-B, respectively when compared with the negative control group.[38] Similarly, both ESWT-exposed groups of PRP also demonstrated significant increases in PDGF-BB (219 and 190%, respectively). Authors subsequently concluded that application of ESWT to PRP increases the expression of growth factors *in vitro*. Given the common clinical scenario where PRP is injected intra-lesionally and followed by ESWT therapy, this investigation provides initial insight into the likely very complex interplay of the two modalities, yet only from an *in-vitro* perspective which cannot be directly extrapolated to the *in-vivo* scenario.

Similar to PRP usage, the simultaneous use of ESWT and bone-marrow derived mesenchymal stem cells (MSCs) is quite frequently utilized for equine orthopedic conditions. When authors investigated the effects of a single ESWT session (cells exposed to 500 pulses at 0.16mJ/mm2 energy, authors appreciated no detrimental effects on cellular proliferation, trilineage capacity or morphology of MSCs.[39] A significant, yet short-lived increase in alkaline phosphatase (ALP) protein expression was appreciated only at day 3, leading authors to conclude that ESWT exposure to MSCs significantly increases osteogenic activity transiently and that higher frequency or ESWT intensity may be required for sustained osteogenic effects. As clinicians continue to utilize both ESWT and MSC therapy for clinical injury, this represents an exciting area of active research.

Safe & Judicious Use of Extracorporeal Shock Wave Therapy:

The major safety concern associated with shock wave therapy has been associated with the period of analgesia following treatment. It has been shown to induce potent analgesia for up

to 4 days in horses. Several theories behind the mechanism of analgesia following ESWT exist. One possible mechanism of analgesia is via neuropeptide depletion. Afferent fibers contain neuropeptides such as substance P and calcitonin gene-related peptide and conduct impulses that lead to the sensation of pain and can contribute to the inflammatory response.[40] These neuropeptides can be released from peripheral nerve endings of nociceptive primary afferent fibers and exert proinflammatory effects in peripheral tissues such as periosteum and joint capsules. Therefore, elimination of primary afferent fibers reduces the pain and inflammatory response. Substance P has been identified in areas of disease in horse which indicates its importance in signaling and maintenance of pain associated with osteoarthritis and other injuries. A direct nerve fiber disruption has not been documented following ESWT.

The short-term analgesic effect of ESWT on 16 horses with PSL pain in a fore or hindlimb was assessed 6, 24, 48 and 72 hours after a single ESWT treatment near the origin of the suspensory ligament (0.15mJ/mm^2, 2000 pules, 35 mm depth).[18] No significant improvements in objective gait parameters were appreciated, but horses with affected forelimbs demonstrated less asymmetry in the contralateral limb. No significant changes in skin sensitivity or thermographic imaging were appreciated, leading authors to conclude that application of one session of ESWT in horses with chronic PSL lameness did not appear to improve lameness in the short-term, and that obvious mechanisms of action were not related to the investigated parameters of objective gait analysis, skin sensation or temperature The authors agree that with currently available shock wave generators, a significant, immediately notable analgesic effect following treatment is not appreciated.[41]

Due to its pain modulation effects, ESWT has been regulated or banned prior to completion by many associations. According to the US Equestrian (USEF), no horse may be treated with shock wave therapy within the 3 days preceding competition. The exception to this rule is that shock wave therapy may be administered by a licensed veterinarian, but no closer than 12 hours prior to competing, and is limited to application to the back and dorsal pelvis areas. Additionally, shock wave therapy is prohibited at Fédération Equestre Internationale (FEI) events and in the 5 days prior to the events. The rules of the National Thoroughbred Racing Association Safety and Integrity Alliance states any treated horse shall not be permitted to race or breeze for a minimum of 10 days following treatment. Furthermore, the used of shock wave therapy is limited to veterinarians only licensed to practice by the commission and the machine must by registered with the commission. Association guidelines regarding the use of ESWT in relation to competition can vary significantly, so close attention must be paid to align with the spirit of competition.

Regulation of the safety and application of ESWT in accordance with sanction guidelines has been difficult because of a lack of a testing mechanism. A recent investigation was performed to evaluate plasma concentrations of 10 inflammatory mediators before and after a single application of ESWT (interleukin (IL) IL-1b, Il-1ra, IL-2, IL-4, IL-6, IL-10, IL-15, interferon gamma, toll-like receptor 2 (TLR2) and TNF-alpha with the goal of determining whether a biomarker relationship for jurisdiction detection could be determined.[42] Authors utilized 11 healthy horses and application of 2700 pulses at energy flux density of 0.55mJ/mm^2, frequency of 3 Hz over an application duration of 15 minutes along the dorsal aspect of the third metacarpal bone. The application of this ESWT protocol was found to significantly downregulate IL1β and IL-6, while significantly upregulating TNFa, IL-1ra and TLR2.[42] While these associations may have been statistically appreciated and certainly warrant further

investigation, it still remains difficult to interpret their significance and repeatability. Additionally, interpretation of these inflammatory mediators' presence in correlation with an athletic horse's age, concurrent orthopedic health/status, exercise level, sedation, other medications, etc. remains unknown. Veterinary prescription and oversight regarding ESWT usage in accordance with jurisdiction rules remains crucial to the safe and judicious use of this technology and its evolving application.

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