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NARRATIVE REVIEW

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Equine shock wave therapy - where are we now?

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Abstract

Over the past three decades, electrohydraulic extracorporeal shock wave therapy (ESWT) as a treatment modality for equine orthopaedic disorders has sparked exponential interest among practitioners, but its clinical applications are quickly evolving and a current review highlighting modernised equine clinical use is lacking. The objective of this review is to summarise the most current ESWT technology, evidence for its use, proposed mechanisms of action and clinical applications in horses while also highlighting the areas requiring further investigation. The three ways to generate a shock wave are through electrohydraulic, electromagnetic or piezoelectric mechanisms, but over the last decade, electrohydraulic systems have predominated due to the ability to focus and control a therapeutic waveform. Shock waves' primary physical effect is believed to be via mechanotransduction leading to cellular activation and downstream signalling. Experimentally, ESWT's effects on osseous, connective tissue and wound healing via various mechanisms of action have been reported both in the human and veterinary literature. Clinical trials have investigated ESWT's orthopaedic application including osteoarthritis, thoracolumbar pain, navicular syndrome, tendinopathy and proximal suspensory desmopathy, with its concomitant use with biologics representing an area of active research. Direct ESWT protocol comparisons in terms of long-term efficacy with variables of energy, depth and exposed tissue types are still lacking with evidence-based recommendations being largely anecdotal. Technical advancements to facilitate the safe and judicious use of ESWT include human and equine hearing protection, light sedation and/or patient restraint. Efforts to ensure the safe and judicious use of ESWT and its analgesic effects are ongoing.

KEYWORDS
horse, shock wave, therapy

1 | INTRODUCTION

Over the past three decades, extracorporeal shock wave therapy (ESWT) as a treatment modality for equine orthopaedic disorders has sparked exponential interest among practitioners. Equine orthopaedic applications include a variety of conditions including osteoarthritis (OA),[1,2] thoracolumbar pain,[3] navicular syndrome,[4,5] tendinopathy[6] and proximal suspensory desmopathy.[7] Despite veterinary use for decades, ESWT's clinical applications are quickly evolving, and a current review highlighting current equine clinical use is lacking. The

objective of this review is to summarise the most current ESWT technology, evidence for its use, proposed mechanisms of action and clinical applications in horses while also highlighting the areas requiring further investigation. Providing a compilation of this information for practicing equine veterinarians will aid in modern clinical decision-making regarding the most up-to-date applications of ESWT.

2 | HISTORY OF EXTRACORPOREAL SHOCK WAVE THERAPY USE IN EQUINE PRACTICE

Lithotripsy was first performed as a non-invasive treatment for urolithiasis in humans, resulting in dramatic resolution of persistent uroliths and ultimately revolutionising the treatment of the disease. As early as World War II it was realised that sound waves had physiologic effects on divers that were exposed to shock waves while in the water when depth charges were being discharged. Subsequently, human patients suffering from hipOA 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 the radiographic bone density of the pelvis following lithotripsy,[8] shock wave therapy began to be formally used for orthopaedic conditions to stimulate tissue and bone formation.[9] The first subsequent musculoskeletal application of ESWT was for healing nonunion long bone fractures.[10,11] A true shock wave for medical purposes has been defined as an acoustic pressure wave characterised by alternating amplitudes of high, rapid (within 1/billionth of a s) positive pressure (10 to a 100) 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.[12]

The purpose of this review is not to exhaust shock wave therapy physics theory, but rather highlight system differences pertinent to the practicing clinician. The three ways to generate a shock wave are through electrohydraulic, electromagnetic or piezoelectric mechanisms.[13] These mechanisms use a capacitor charged at different voltages to rapidly discharge energy within the transducers. All of these mechanisms convert electrical energy into some form of a pressure wave that then travels through fluid and soft tissue to release kinetic energy at tissue interfaces, but the three mechanisms vary substantially in the size of the focal point, energy densities and subsequent total energies being delivered to the desired treatment area.[9] Historically, all three mechanisms have been used in veterinary medicine, but over the last decade, electrohydraulic systems have predominated due to the ability to focus and control a therapeutic waveform. A synopsis of technology differences can be found in supplementary item 1. In this review, ESWT will refer to electrohydraulic ESWT unless otherwise noted.

3 | UPDATES ON TISSUE 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 signalling. Mechanotransduction describes the cellular processes that translate mechanical stimuli into biochemical signals, enabling cells to adapt to their environment.[14] The initiation of the signalling pathways results in the ultimate biological outcomes seen with shock wave therapy including control of inflammation, angiogenesis, and stimulation of cytokine production.[12] Early ESWT studies in murine and human models found increases in the expression of favourable cytokines associated with improved healing responses (specifically transforming growth factor-beta [TGF-β1] and vascular endothelial growth factor-A [VEGF-A]).[15] Studies in horses have also noted the upregulation of beneficial anabolic cytokines following ESWT.[16,17]

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

Early studies found increases in the 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.[15] 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.[18] 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 4 weeks after the last ESWT treatment compared with the untreated contralateral limb.[18] In a wound model in horses that were treated with a lower EFD (0.11 mJ/mm^2) immediately, and then on study Days 7, 14 and 21 post-wound induction, there was no increase in TGF-β1 and only an increase in IGF-1 from 28 days onward.[19] The lack of increased TGF-β1 could be that the macrophages in the wound model were already stimulated or that the shock wave therapy protocol used was not sufficient to stimulate 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.[20] Specifically, a rat hindlimb ischaemia 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.[21] Notably, it was determined that shock waves 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 maximise the desired outcomes and incorporate into clinical use.

4 | EXPERIMENTAL TRIALS RELEVANT TO CURRENT CLINICAL USE

4.1 | Effects on bone healing

The early adoption of human musculoskeletal ESWT application was to stimulate bone healing[8] with subsequent human and equine studies confirming that ESWT beneficially stimulates bone remodelling. In a study evaluating the capacity of ESWT to stimulate bone healing and/or production of microfractures, one metacarpus of four horses was treated with 1000 pulses at 0.89 mJ/mm^2 and the opposite treated with 1000 pulses at 1.8 mJ/mm^2 with a focused electrohydraulic generator (Table 1).[9] Exposure to higher than usual EFDs was used to determine if energy levels higher than typical clinical use would induce microfractures or damage that could result in bone failure. Histologically, no damage to the bone or soft tissue in the treatment field was appreciated using either ESWT exposure setting.[9]

The effect of shock waves on the microstructure of bone has also been evaluated by determining the modulus of elasticity of the bone via ultrasound velocity and subsequent microfracture staining.[22] Milled dorsal cortical bone specimens were treated with 500 pulses of ESWT at 0.15 mJ/mm^2. The ultrasound velocity through the bone was determined and used to calculate the modulus of elasticity. The samples were then further sectioned and stained to determine if microcracks were evident histologically. At these treatment parameters, there was no effect on the modulus of elasticity nor was their evidence of microfractures histologically.[22]

In a pilot study of two horses in which one dorsal metacarpus was treated with 2000 pulses at 0.89 mJ/mm^2 (the contralateral metacarpus was left untreated), the shock wave-treated metacarpal bones had 30% more activated osteons extending from the periosteal to the endosteal surface.[9] Similarly, osteogenesis was stimulated by the application of 2000 pulses at 0.15 mJ/mm^2 to the proximal fourth metacarpal bone.[23] Shock wave therapy was demonstrated to increase the number of osteoblasts present and increase radionucleotide uptake following treatment of 2000 pulses at 0.15 mJ/mm^2.

Also noteworthy, there have been two studies on the effect of shock waves on the joint and subchondral bone. Shock wave therapy was administered 14 and 28 days following the surgical creation of an osteochondral fragment in the carpi of horses.[16] No effect on bone density, microdamage, trabecular thickness or mineral apposition rate was appreciated.[16] There was, however, an increase in serum biomarkers indicative of bone remodelling (specifically osteocalcin and C-terminal telopeptide of type 1 collagen). In the same osteochondral fragment model with the same treatment parameters, ESWT was found to significantly decrease lameness scores associated with OA.[24] Specifically, lameness was decreased 1.7-fold in treated carpi at Day 14 (lameness score of 1.25 ± 0.19 in ESWT-treated carpi compared with 2.13 ± 0.19 in placebo-treated carpi).[24] This effect was maintained through the end of the study at day 70 in treated horses.[24]

4.2 | Effects on soft tissue healing

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 eight dogs.[25] The ESWT-exposed sites demonstrated significantly more neovascularisation than those not receiving ESWT.[25]

In horses there are two studies that have evaluated the effects of ESWT on collagenase-induced SDF tendonitis (Table 1).[26,27] Both studies used 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 fibres in one study,[27] while a clear and significant increase in neovascularisation of the treated tendon was appreciated in the other study.[26] 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.[28,29] 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[29] while McClure et al. found a greater amount of proteoglycan deposition within the collagen matrix.[28]

4.3 | Effects on wound healing

Several studies performed on human, rat and swine wounds have described beneficial effects of ESWT including increased rate of

TABLE 1 Summary of experimental trials relevant to current clinical use investigating the effects of extracorporeal shockwave therapy (ESWT) for treatment of a variety of orthopaedic conditions

Investigator	Orthopaedic condition	Model	Number of horses in study	Energy flux density (EFD)	Interval of treatments	Measurement outcomes	Pulses and probe
Frisbie et al. 2009[24]	Experimentally induced carpal OA	VersaTron	$n = 8$	0.14 mJ/mm^2 & 0.15 mJ/mm^2	Two treatments at 14-day intervals	Lameness improvement	2000 pulses 1st treatment; 1500 pulses 2nd treatment
Kawcak et al. 2011[16]	Experimentally induced carpal OA	VersaTron	$n = 8$	0.14 mJ/mm^2 & 0.15 mJ/mm^2	Two treatments at 14-day intervals	No effect on subchondral bone; increased serum biomarkers indicative of bone remodelling	2000 pulses 1st treatment; 1500 pulses 2nd treatment
Kersh et al. 2006[26]	Induced superficial digital flexor tendonitis	Equitron	$n = 6$	0.14 mJ/mm^2	Three treatments at 3-week intervals	Histologically increased neovascularisation	500 pulses with 5 mm probe
McClure et al. 2004[9]	Effect on bone – metacarpus and metatarsus	Orthowave electrohydraulic system	$n = 4$	0.89 mJ/mm^2 & 1.8 mJ/mm^2	One treatment	Osteogenesis reported without causing microfractures	1000 pulses dorsal aspect of the mid-diaphysis MC3 and MT3
McClure et al. 2004[28]	Induced suspensory ligament desmitis	Equitron	$n = 4$	0.14 mJ/mm^2	Three treatments at 3-week intervals	Improved the rate of healing as assessed ultrasonographically	1500 pulses total (500 each medially and laterally with 5 mm probe and 500 pulses along palmar aspect with 35 mm probe)
Alves et al. 2006[27]	Induced superficial digital flexor tendonitis	VersaTron	$n = 10$	0.15 mJ/mm^2	Three treatments at 3-week intervals	Improved fibre alignment faster	1500 pulses total (500 medial, lateral and palmar) with 5 mm probe
Caminoto et al. 2005[29]	Induced hindlimb suspensory ligament desmitis	VersaTron	$n = 10$	0.15 mJ/mm^2	Three treatments at 3-week intervals	Collagen fibril formation and greater expression of transforming growth factor β-1	1500 pulses total (500 each medially and laterally with 5 mm probe and 500 plantar aspect with 35 mm probe)
Pauwels et al. 2004[22]	Milled dorsal cortical bone specimens	Equitron	$n = 8$	0.15 mJ/mm^2	One treatment	No evidence of microfractures histologically	500 pulses with 5 mm probe
Ringer et al. 2005	Effect on bone - origin of the SL at MC3 and the MT4	Equitron	$n = 6$	0.15 mJ/mm^2	Two treatments at 16-day intervals	Activation of osteons	2000 pulses with 35 mm probe at origin of the SL on MC3 and 2000 pulses with 5 mm probe on MT4
Bischofberger et al. 2006[23]	Histological effect on bone - origin of the SL at MC3 and the MT4	Equitron	$n = 6$	0.15 mJ/mm^2	Two treatments at 16-day intervals	No evidence of microfractures histologically	2000 pulses with 35 mm probe at origin of the SL on MC3 and 2000 pulses with 5 mm probe on MT4

TABLE 1 (Continued)

Investigator	Orthopaedic condition	Model	Number of horses in study	Energy flux density (EFD)	Interval of treatments	Measurement outcomes	Pulses and probe
Johnson et al. 2010[36]	Wound healing	Sanuwave	$n = 1$	0.11 mJ/mm^2	Four treatments total; 11-, 19-, 26- and 41-days post burn	No adverse effects and decreased pruritus	4500 pulses with 5 mm probe over burn area
Morgan et al. 2009[35]	Induced full thickness wound on dorsomedial metacarpus and metatarsus	Equitron	$n = 6$	0.11 mJ/mm^2	Weekly intervals until wounds healed	Shorter healing time	500 pulses on metacarpal wound, 280 pulses on metatarsal wounds
Silveira et al. 2010[34]	Induced superficial wounds on metacarpus	Electrohydraulic shock wave generator with wide-focused applicator CP 155	$n = 6$	0.11 mJ/mm^2	One treatment	Less exuberant granulation tissue and appeared healthier	625 pulses over wound
Link et al. 2013[19]	Wound healing on distal limb	Electrohydraulic shock wave generator with wide-focused applicator CP 155	$n = 8$	0.11 mJ/mm^2	One treatment	Less exuberant granulation tissue and improved wound healing on distal limb	900 pulses

epithelialisation 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 the healing of diabetic ulcers and other wounds led to the evaluation of ESWT for wound healing. In a study evaluating the repair of partial thickness wounds in pigs, researchers found that the effect of ESWT on the rate of epithelialisation 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-epithelialisation in human patients with deep partial-thickness burns has been an ongoing source of investigation.[32] In a multicentre randomised, 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 (Table 1). 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 epithelialisation, 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.[35] 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.[19] It was hypothesised that the decrease in TGF-β1 may decrease exuberant granulation tissue. Lastly, a single case report that used ESWT for adjunct treatment of an extensive burn injury over the dorsum of a horse documented no adverse effects and a decrease in pruritus.[36]

As mechanistically-driven experiments continue to investigate the physical effects of ESWT, further insight regarding its role in inflammation modulation, angiogenesis, and stimulation of cytokine production can be expected. As reported thus far, beneficial effects on osseous, soft tissue and wound healing via various mechanisms of action have been reported both in the human and veterinary literature. These early experimental investigations have inspired several clinical trials that continue to shape the use of ESWT in equine practice.

5 | CLINICAL TRIALS RELEVANT TO CURRENT CLINICAL USE

5.1 | Proximal suspensory desmopathy

One of the most common clinical applications of ESWT is for the treatment of both forelimb and hindlimb proximal suspensory desmopathy.[7,37–40] 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 1 year after diagnosis.[38] Authors used 2000 pulses at an EFD of 0.15 mJ/mm^2 every 3 weeks for a total of three treatments (Equitron, HMT/Switech Medical) in addition to stall rest and a 3-month controlled exercise program. Nearly 62% of forelimb proximal suspensory ligament (PSL) desmopathy cases had returned to full work by 6 months, and roughly 56% were still in full work 1 year after diagnosis. In contrast, only roughly 41% of hindlimb PSL cases had returned to full work by 6 months, which decreased to 18% 1 year after diagnosis, highlighting the frustrating reoccurrence of hindlimb PSL desmopathy.[38]

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 (Table 2).[37] Specifically, 41 horses underwent surgery with 24 returning to their previous level of work at an average of 10.1 months.[37] This was in comparison to 34 horses that received ESWT only with 20 returning to their previous level of work at an average of 7 months.[37] Fifteen of the 75 cases remained lame despite surgery or ESWT alone, so a combination of surgery and ESWT was eventually used, with seven of those 15 refractory cases returning to work in 18 months.[37] As an acknowledged (common) limitation, the inclusion of a control group may have helped obviate treatment-specific differences more clearly.

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 randomised clinical trial, horses treated with ESWT were 3.8 times more likely to return to work at 1 year compared with PRP-treated horses, regardless of baseline ultrasound severity.[7] Interestingly, horses treated with ESWT demonstrated greater lameness improvement compared with PRP at 4 days post treatment, but at 1 year, horses with more severe ultrasound changes responded better to PRP.[7] Authors concluded that both PRP and ESWT can be expected to yield favourable therapeutic responses in western performance horses, but baseline ultrasound severity assessment may help guide treatment selection.[7]

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 standardised clinical trials for a more direct comparison of treatment-specific effects across a variety of injuries.[40] As clinical use often supersedes scientific validation, specific, evidence-based protocol recommendations are still lacking, but would be beneficial to the practicing clinician. In a subsequent meta-analysis evaluating a return to function rates in horses with PSL desmopathy treated with ESWT compared with 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.[41]

In the authors' experience, delivery of 800 pulses at an energy setting of E6 (EFD of 0.33 mJ/mm^2) with a 20 or 35 mm probe in a non-weight bearing position at weekly intervals for 3 weeks represents the most commonly used initial protocol for the management of forelimb and/or hindlimb proximal suspensory desmopathy, which varies slightly from protocols used in research studies. Protocols in current clinical usage are published by commercial ESWT providers (PulseVet User Manual, 2022). It may also be beneficial to incorporate the use of ultrasound-guidance to further anatomically direct ESWT treatment. A general guideline is that if one can clearly visualise the treatment site with ultrasound one can effectively treat with ESWT. With the continued use of advanced imaging techniques such as magnetic resonance imaging (MRI), the clinician's ability to characterise the spectrum of injury within these dense anatomic regions (metatarsus/tarsus and metacarpus/carpus) has improved considerably,[42,43] but also obviated diagnostic vulnerability for ESWT clinical trials in which advanced imaging was not used to characterise the original injury. Inherently unknown differences in original lesion size, extent, severity and configuration that would ultimately affect treatment responses limit direct comparisons between studies. Furthermore, discipline-specific injury patterns are now reported[43] which may explain perceived varied treatment responses between horses of different athletic disciplines (western performance compared with English sport horses, for example).

5.2 | Navicular disease

Navicular disease in the equine athlete continues to represent a challenging source of lameness often involving pathologic changes of the fibrocartilage of the navicular bone, the deep digital flexor tendon and/or the navicular bursa. When the clinical effectiveness of ESWT for the 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 (Table 2).[4] Navicular bone ESWT was performed using an electrohydraulic system (Orthowave, Medical Technologies & Services) while the horses were under general anaesthesia in lateral recumbency.[4] 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).[4] The treatment protocol and positioning was based on the shock wave generator being used. The coupler was on an articulating arm that was not feasible to

TABLE 2 Summary of clinical trials relevant to current clinical use investigating the effects of extracorporeal shockwave therapy (ESWT) for treatment of a variety of orthopaedic conditions

Investigator	Condition	Model	Number of horses in study	Energy flux density (EFD)	Interval of treatments	Measurement outcomes	Pulses and probe
Lischer et al. 2006[38]	Proximal suspensory ligament desmopathy	Equitron	$n = 34$ forelimb $n = 22$ hindlimb	0.25 mJ/mm^2	Every 21 days (total 3 treatments)	62% forelimb and 41% hindlimb returned to full work by 6 months	2000 pulses
Norvall et al. 2015[37]	Hindlimb proximal suspensory ligament desmopathy	Versatron	$n = 34$	0.33 mJ/mm^2	3-week intervals for total of 3 treatments	59% returned to previous level of work average 7 months	1000 pulses with 35 mm probe
Giunta et al. 2019[7]	Proximal suspensory ligament desmopathy	VersaTron	$n = 49$ (14 forelimb, 35 hindlimb)	0.33 mJ/mm2	1-week intervals for total of 3 treatments	76% in work at 1 year post treatment	800 pulses with 20 mm probe
McClure et al. 2004[12]	Navicular disease	Orthowave electrohydraulic system	$n = 27$	0.89 mJ/mm^2	1 treatment	56% lameness decreased by blinded evaluator	1000 pulses through frog and 1000 pulses at heel
McCaroll et al. 2000[1]	Hock bone spavin	EvoTron	$n = 74$	22 kV	One treatment	80% had lameness grade decreased by at least 1 grade	2000 pulses at affected distal tarsal joints
Trager et al. 2020[3]	Thoracolumbar pain	VersaTron	$n = 12$	0.13 mJ/mm^2	Every 14 days (total 3 treatments)	Pain modulation	80 mm probe 1500 pulses
McClure et al. 2003	Dorsal spinus process impingement and dorsal articular process OA	Equitron	N/A; Clinical impression description only	0.15 mJ/mm^2	One treatment at 2–4 week intervals for a total of 3 months	Pain modulation	For each 1 cm in length, 50 pulses delivered from each side (total of 100 pulses) at each site of radiographic lesion with 35 or 80 mm probe
Allen et al. 2010[47]	Dorsal spinus process impingement and dorsal articular process OA	VersaTron and Equitron	$n = 115$, $n = 74$ for follow-up data	0.33 mJ/mm^2	One treatment	Pain modulation	1000–2000 pulses with 35 mm probe axially and abaxially for spinous process impingement and 80 mm probe for dorsal articular process

use in standing horses but was equipped with a targeting mechanism as would be used for lithotripsy. Following treatment, horses were stall rested for 1 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.[4]

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 characterisation. Given that transient cutaneous analgesia persisting only a few days has been reported,[44,45] the clinician longitudinally monitoring therapeutic responses to ESWT therapy in conjunction with graduated, controlled exercise programs can use this information to gauge long-term clinical progression and further guide return-to-work schedules. Additionally, modern ESWT generators have improved subjective clinical responses (albeit temporarily) due to the ability to deliver higher EFD than original portable units.

5.3 | Distal tarsal osteoarthritis

Distal tarsal osteoarthritis (OA), partial to complete ankylosis and the spectrum of pathologic changes in between still represent 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.[2,46] When the effectiveness of ESWT for the treatment of bone spavin in 74 horses was evaluated, the application of 2000 pulses at 0.89 mJ/mm^2 to the affected joints decreased lameness grade by at least one in 80% of the horses (Table 2).[1] Horses were diagnosed with bone spavin by lameness evaluation, flexion tests, diagnostic anaesthesia 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.[1] Interestingly, follow-up radiographs demonstrated no consistent changes when compared with 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.

In the authors' current opinion, delivery of 1000–1200 pulses at E6 (0.33 mJ/mm^2) with a 20 mm or 35 mm probe along the most affected regions of OA/ankylosis (typically the dorsomedial aspect) at weekly intervals for 3 weeks is beneficial, which can be strategised in between and/or in conjunction with intra-articular (IA) hock injections. Interestingly, it is also the authors' experience that ESWT when applied to clinically active distal tarsal OA/ongoing remodelling consistently elicits a painful response (particularly along the medial aspect of the tarsus) which is otherwise not appreciated during ESWT sessions of other anatomic regions. While not formally reported to date, ESWT for management of OA of other joints (fetlocks, stifles, carpus, cervical spine) has also yielded subjectively favourable, yet transient responses (in the authors' clinical experience).

5.4 | Thoracolumbar pain

Two anecdotally reported ESWT guidelines for spinous process impingement (SPI) and dorsal articular process (DAP) OA have been published (Table 2).[47,48] McClure et al. used 50 pulses at an energy setting of 0.15 mJ/mm^2 with a 35 or 80 mm probe on the left and right sides every 1 cm for the length of spinous process sclerosis.[48] Allen et al. described applying 1000–2000 pulses with a 35 mm 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 80 mm probe for DAP.[47] These sessions were then followed by 2 days of athletic rest, then 3–5 days of gradually returning to exercise.[47] A recent non-randomised clinical trial by Trager et al. used 1500 pulses with an 80 mm 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.[3] The generator was oriented adjacent to the 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.[3]

The current authors' tend to use pulses (1000–2000 total) with a combination of both the 35, 80 mm probe or recently developed wider focused generator (Xtrode, proprietary probe of PulseVet Technologies, LLC) globally and/or targeted at specific areas of clinical sensitivity/radiographic change. Additionally, the authors herein feel that subjective improvements in pain related to the sacroiliac and cervical regions are also able to be more effectively managed with ESWT, making it a non-invasive way to manage pain of the axial skeleton when combined with physiotherapeutic exercises and other pain modulation therapeutics.

6 | SAFE AND 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.[49] Several theories behind the mechanism of analgesia

following ESWT exist. One possible mechanism of analgesia is via neuropeptide depletion. Afferent fibres 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.[49] These neuropeptides can be released from peripheral nerve endings of nociceptive primary afferent fibres and exert proinflammatory effects in peripheral tissues such as periosteum and joint capsules. Therefore, elimination of primary afferent fibres reduces the pain and inflammatory response. Substance P has been identified in areas of disease in the horse which indicates its importance in signalling and maintenance of pain associated with OA and other injuries.[49] A direct nerve fibre disruption has not been documented following ESWT.[49]

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 h after a single ESWT treatment near the origin of the suspensory ligament (0.15 mJ/mm^2, 2000 pules, 35 mm depth).[39] No significant improvements in objective gait parameters (stride frequency, stance duration, vertical impulse, peak vertical force) were appreciated, but horses with affected forelimbs demonstrated less weight-bearing gait asymmetry indices (ASI) in the contralateral limb.[39] 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.[39] The authors agree that with currently available shock wave generators, a significant, immediately notable analgesic effect following treatment is not appreciated.[44]

Due to its pain modulation effects, ESWT has been regulated or banned prior to competition by many associations. According to the US Equestrian (USEF), no horse may be treated with shock wave therapy within the 3 days preceding competition.[50] The exception to this rule is that shock wave therapy may be administered by a licensed veterinarian, but no closer than 12 h 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.[51] 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 use of shock wave therapy is limited to veterinarians only licensed to practice by the commission and the machine must by registered with the commission.[51,52] 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.[17] Authors used 11 healthy horses and application of 2700 pulses at an energy flux density of 0.55 mJ/mm^2, frequency of 3 Hz over an application duration of 15 min 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.[17] 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 orthopaedic health/status, exercise level, sedation, other medications, and so forth 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.

7 | APPLICATION OF EXTRACORPOREAL SHOCK WAVE THERAPY: TIPS TO OPTIMISING TREATMENT DELIVERY

Safe, efficient application of ESWT can often be facilitated with light, standing sedation (as permitted under sanction guidelines for actively competing horses), patient restraint and potentially ear plugs particularly in rooms with tiled or stone walls that amplify noise reverberation. The use of ear plugs/hearing protection for the veterinarians/technicians administering the ESWT and/or holding the equine patient has also been advised due to the loud, ballistic noise generated and its potential (although unproven) ability to induce hearing loss.[53] Patient preparation involving cleaning and/or washing of the skin/hair, light debris removal and generous gel application is advised because any air between the shock wave membrane and the skin will limit energy transmission. Depending on the horse and season, clipping of the hair may not be necessary.

More frequently, veterinarians are applying ESWT with the limb in a flexed, non-weight bearing position to facilitate more targeted tissue application. Specifically, ESWT for the treatment of proximal suspensory desmopathy (both forelimb or hindlimb), fetlock OA (particularly along the dorsomedial aspect of the proximal phalanx), third carpal bone subchondral bone injury (along the radial facet) and medial femoral condyle subchondral bone defects can be facilitated anatomically with the limb gently flexed or in a static, non-weight bearing position (Figure 1). Obvious safety considerations must be given to patient selection for non-weight bearing positioning, but subjective improvements in probe placement to facilitate anatomic accessibility of certain regions can be accomplished through incorporation of varied limb placement techniques during the application of ESWT.

In veterinary cases with orthopaedic metal implants, ESWT has been successfully used to accelerate boney healing.[54] It is important to note, however, that the energy produced by the ESWT probe will not traverse through the implant, but rather be reflected around and under the adjacent tissue. Further, maximal reflection only occurs

when the tissue implant interface is perpendicular to the direction of travel of the shock wave. In absence of tangential electrode-to-implant placement, the wave front will refract and disperse to variable extents which can consume energy and therefore markedly reduce the energy of the shock wave.[13] For this reason, approaching the anatomic region of interest from the opposite side of the implant is advised to ensure that the energy will reflect across the tissue adjacent to the implant.[54]

Published data regarding recommended number of pulses, pulse frequency, energy flux density and probe selection for specific injuries are unfortunately still lacking for ESWT, although anecdotal use seems to reflect protocols similar to or modified from those used experimentally and provided by commercial ESWT providers (PulseVet User Manual, 2022). Pulse frequency specifically has been shown to increase cavitation,[55] and historically microbubble formation has been thought to aid in the pulverisation of urinary stones yet also possess the potential to cause tissue damage due to the fact that cavitation bubbles create and release UV light, extreme temperatures and localised powerful jet streams (albeit on a microscopic scale).[56] Because ultrasonic waves are delivered over a much longer period of treatment time than that of shock waves, the biological dangers of cavitation produced during ESWT are considerably less than that of ultrasound therapy,[56] which must also be taken into consideration. To date, no studies exist that demonstrate pulse frequency, subsequent microbubble and ensuing cavitation formation's effect on clinical efficacy of ESWT. With the ongoing interest and continued clinical use of ESWT, further evidence-based refinements in protocol specifications can be expected.

8 | EXTRACORPOREAL SHOCK WAVE THERAPY AND BIOLOGIC THERAPIES

With the increasing use of biologic therapies in the treatment of equine orthopaedic 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[57] 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.[57] Specifically, three treatment groups were used 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.[57] 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 investigating if application of shock waves either with a 'standard' (2 cm focal width and medium energy density) or a 'power' (1 cm focal width and higher energy density) probe to PRP samples increased the concentration of TGF-β and platelet-derived growth factor BB (PDGF-BB), 46 and 33% significant increases in TGF-β, respectively were noted when compared with the negative control group.[58] Similarly, both ESWT-exposed groups of PRP also demonstrated significant increases in PDGF-BB (219 and 190%, respectively).[58] Authors subsequently concluded that the application of ESWT to PRP increases the expression of growth factors in vitro. Given the common clinical scenario where PRP is injected intralesionally 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 used for equine orthopaedic conditions. When authors investigated the effects of a single ESWT session (cells exposed to 500 pulses at 0.16 mJ/mm^2 energy) authors appreciated no detrimental effects on cellular proliferation, trilineage capacity or morphology of MSCs.[59] 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.[59] As clinicians continue to use both ESWT and MSC therapy for clinical injury, this represents an exciting area of active research.

9 | EMERGING APPLICATIONS OF EXTRACORPOREAL SHOCK WAVE THERAPY FOR USE IN THE HORSE

Several emerging, yet only anecdotally described applications for ESWT are in current clinical use by the authors and other practicing equine veterinarians (M. Tanner, personal communication, 2021). Of specific interest is the application of ESWT over lung surfaces as a treatment for exercise-induced pulmonary haemorrhage (EIPH) and/or pleurodynia. Applying ESWT over gas-filled cavities like lung or intestine has classically been described as strictly contra-indicated due to the acoustic impedance of air being markedly lower than the acoustic impedance of soft-tissue such as muscle.[60] Subsequently, all acoustic energy is thought to tangentially reflect at the border zone and therefore, maximum pressure may turn into rarefaction pressure up to twice the extent of the former pressure wave and result in considerable tissue damage at the border zone.[60] Considering that application of ESWT as a treatment for back pain likely infringes anatomically on caudal-dorsal lung fields, its inadvertent application to the dorsal pleural surface region has likely already been unintentionally applied for several years. In an unpublished study from the University of Cordoba, ESWT was applied to equine thoraces in horses subjected to euthanasiafor reasons unrelated to respiratory dysfunction (A.M. Juzado, unpublished data, 2021) At a range of pulses applied at two intercostal spaces of two horses

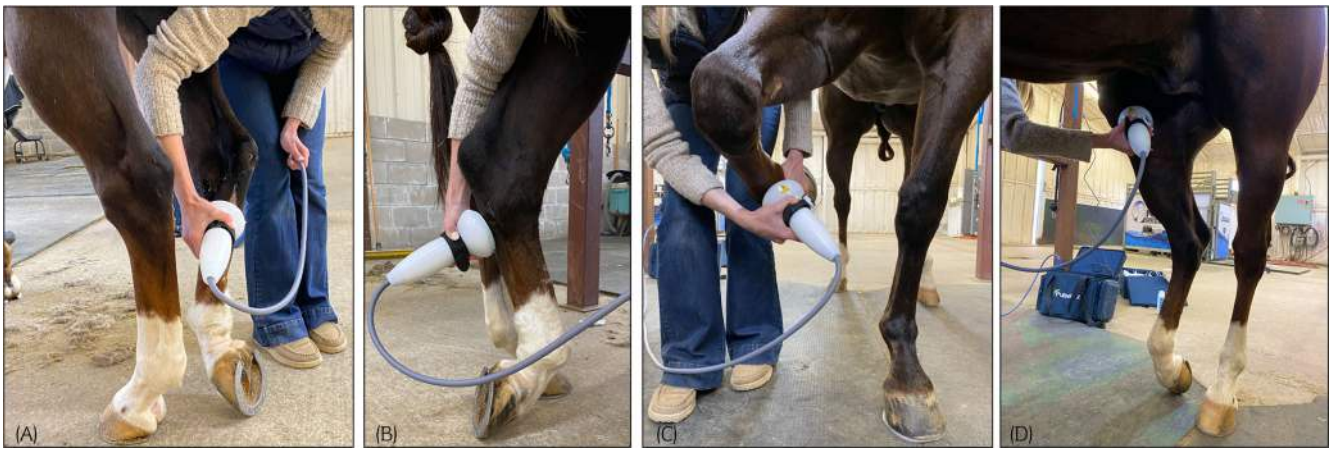

FIGURE 1 Extracorporeal shock wave therapy (ESWT) being performed in non-weight bearing (NWB) positions on the right hind proximal suspensory ligament (A, B), the right front fetlock along the medial condyle (C) and the right hind medial femoral condyle (D). More frequently, veterinarians are applying ESWT with the limb in a flexed, or NWB position to facilitate more targeted tissue application.

(1000–3000 total pulses), subjective gross histologic assessment did not indicate pathologic change to the thoracic wall and mild, limited hyperemia of the pleural surface (A.M. Juzado, unpublished data, 2021). While these pilot findings do not constitute formal investigation or safety advocation, they do represent an initial attempt to quantify gross histologic change secondary to ESWT exposure that warrants further investigation. At the date of publication, these reports are only anecdotal, thus conclusions regarding potential mechanism of action, efficacy, long-term safety and pain modulation must be cautiously interpreted.

Lastly, it is the clinical impression of the author that pain (pleurodynia) associated with pleural disease (intra-thoracic masses, pleuropneumonia, pleuritis, pleural effusion, etc.,) can manifest itself in varying degrees of forelimb lameness, poor performance or general malaise in the equine athlete [S. Johnson, personal communication, June 2022]. Similar to reports of ESWT in the use of EIPH, ESWT used for thoracic sling/girdle pain modulation has been anecdotally used without appreciated clinical complications (1000 pulses applied along intercostal spaces, E6, 80 mm probe as once/week treatments for a total of three treatments). Subjective clinical improvements in appetite, general attitude and forelimb lameness have been appreciated 1–3 weeks following initial treatment (S. Johnson, personal communication, June 2022). Patient preparation is similar to that described above, with generous amounts of gel used, and ultrasound evaluation guiding anatomic sites of pulse application. Given that pleurodynia plays a significant role in subsequent systemic health (appetite, lethargy, pain, etc.,) of a variety of pleural diseases, the investigation of ESWT for pain modulation to improve general systemic health in cases of respiratory dysfunction and/or pleurodynia warrants further investigation. It is also noteworthy to acknowledge that ESWT's effects on primary pulmonary disease processes remains unknown, and with this pain modulation application still in its infancy, caution regarding pleural ESWT application is still warranted. Lastly, research is ongoing regarding the application of ESWT for sarcoid lesion management. Further work is expected, but preliminary results suggest that lesion size reduced and even resolved in clinical cases thus far (J. Will, unpublished data, 2021), with further formal investigations expected.

10 | CONCLUSION

Electrohydraulic ESWT continues to be heavily used for the management of a variety of orthopaedic injuries in horses, and its concomitant use with other biologics is an area of active research. Direct ESWT protocol comparisons in terms of long-term efficacy following exposure to various tissue types and depths are still lacking with evidence-based recommendations being limited due to inherent differences in study design, employed ESWT protocol and evaluation parameters. Suggested protocols are available from commercial ESWT providers. Technical advancements to facilitate the safe and judicious use of ESWT include human and equine ear plugs, light sedation and/or patient restraint. Equine veterinarians remain focused on ensuring the prudent application of ESWT in accordance with sanction guidelines. Efforts to detect ESWT's inappropriate prescription and/or use by non-veterinarians are ongoing. Shock wave therapy to multi-modally treat a variety of equine respiratory dysfunctions is an exciting, yet not formally investigated the proposed application of ESWT.

AUTHOR CONTRIBUTIONS

Sherry A. Johnson and Scott R. McClure contributed to study conception and design, acquisition of data, analysis and interpretation of data, drafting the manuscript and revising it for intellectual content. Roderick B. Richards and Angie M. Esselman contributed to the acquisition of data, analysis and interpretation of data, drafting of the manuscript and revising it for intellectual content. David D. Frisbie contributed to the analysis and interpretation of data, drafting the manuscript and revising it for intellectual content. All authors gave their final approval of the manuscript.

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CONFLICT OF INTEREST STATEMENT

S. Johnson, S. McClure and D. Frisbie are members of the equine advisory board of PulseVet Technologies, LLC. R. Richards is the director of international business and clinical research of PulseVet Technologies, LLC.

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Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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