Determination of functional and morphologic changes in palmar digital nerves after nonfocused extracorporeal shock wave treatment in horses

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Objective—To determine functional and morphologic changes in palmar digital nerves after nonfocused extracorporeal shock wave (ESW) treatment in horses.

Animals—6 horses.

Procedures—The medial and lateral palmar digital nerves of the left forelimb were treated with nonfocused ESWs. The medial palmar digital nerve of the right forelimb served as a nontreated control nerve. At 3, 7, and 35 days after treatment, respectively, 2 horses each were anesthetized and nerves were surgically exposed. Sensory nerve conduction velocities (SNCVs) of treated and control nerves were recorded, after which palmar digital neurectomies were performed. Morphologic changes in nerves were assessed via transmission electron microscopy.

Results—Significantly lower SNCV in treated medial and lateral nerves, compared with control nerves, was found 3 and 7 days after treatment. A significantly lower SNCV was detected in treated medial but not lateral nerves 35 days after treatment. Transmission electron microscopy of treated nerves revealed disruption of the myelin sheath with no evidence of damage to Schwann cell bodies or axons, 3, 7, and 35 days after treatment.

Conclusions and Clinical Relevance—Nonfocused ESW treatment of the metacarpophalangeal area resulted in lower SNCV in palmar digital nerves. This effect likely contributes to the post-treatment analgesia observed in horses and may result in altered peripheral pain perception. Horses with preexisting lesions may be at greater risk of sustaining catastrophic injuries when exercised after treatment. (*Am J Vet Res* 2004;65:1714–1718)

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Extracorporeal shock wave (ESW) treatment is a newly adapted technique used to treat musculoskeletal disorders in horses.[1] In several case series in which ESWs were used, successful treatment of soft tissue and bone disorders including proximal suspensory desmitis,[2,3] dorsal metacarpal disease,[4] navicular disease,[5] and osteoarthritis of the tarsometatarsal and distal intertarsal joints was reported.[6] Although few controlled studies have been performed and the specific mechanism by which shock waves affect tissues still needs to be elucidated, ESW treatment has become increasingly popular in equine practice.

Extracorporeal shock waves are pressure gradient waves that have a rise time of 5 to 10 nanoseconds and a peak pressure of up to 100 MPa, followed by a rapid decrease to negative pressure, before a return to baseline in a total pulse time of approximately 300 nanoseconds.[1,7] Wave energy is released at interfaces of tissues that have different acoustic impedances and results in compression and shear loads on the surface of the material with the greater impedance. These loads result in a process referred to as cavitation, which is caused by the development and collapse of microscopic gas bubbles in the interstitial fluid of tissues. When gas bubbles develop near an acoustic boundary layer, they invert asymmetrically and a small jet of fluid impinges on the surface of the material with greater impedance at a velocity of several hundred meters per second, thereby generating high localized stresses.[7]

Two fundamentally different techniques are used to generate ESWs. Focused shock wave generators were originally developed for noninvasive destruction of urinary calculi in humans[8] and were subsequently adapted to treat a variety of musculoskeletal disorders.[9,10] Focused shock wave generators initiate a pressure wave within a fluid medium and focus the wave via reflection within the generator toward a focal point in the patient.[7] Nonfocused ESWs or radial pressure waves are generated via mechanical concussion. They are characterized by lower energies than those of focused shock waves, a slower rise time, and a negative component that is of the same magnitude as the positive component. Their maximum wave energy is found at the applicator-skin interface; this energy decreases rapidly in proportion to the distance from the generator.[1]

Treatment with focused and nonfocused ESWs can induce analgesia. This analgesic effect is likely independent of any other potential beneficial effects on tis-

sue healing and is observed rapidly after treatment. Results of studies in humans[9,10] and horses[2,4,6] reveal abatement of various painful orthopedic conditions; however, no concurrent radiographic changes are evident. Analgesia of an injured limb is of concern in an equine athlete because it disables protective limiting mechanisms and may place horses with preexisting lesions at greater risk of sustaining catastrophic injury when exercised with altered peripheral pain perception. This problem has been recognized by the equine industry and has led to the development of regulations concerning the use of ESW treatment prior to competition by racing jurisdictions and the Federation Equine International.[1]

Extracorporeal shock wave treatment does not appear to be used to specifically treat peripheral nerves in humans. In horses, nerves of the distal portion of the limb are often treated directly to provide relief in painful syndromes of the foot such as navicular disease.[5] To the authors' knowledge, there are no reports of the effects of ESW treatment on function and morphologic features of peripheral nerves in horses.

The purposes of the study reported here were to determine functional changes in palmar digital nerves after treatment with nonfocused ESWs by use of **sensory nerve conduction velocity (SNCV)** measurements and describe morphologic changes in ESW-treated nerve segments via **transmission electron microscopy (TEM)**. We hypothesized that a single treatment with nonfocused ESWs applied directly over a peripheral nerve would result in lower SNCV and noticeable morphologic changes in the nerve.

Materials and Methods

Horses—The study was approved by the Institutional Animal Care and Use Committee of Louisiana State University. Six horses were used in the study. Two Quarter Horses and 4 Thoroughbreds (4 geldings and 2 mares) with mean ± SD (range) weight of 514 ± 43.6 (464 to 584) kg and mean ± SD (range) age of 13.8 ± 4.47 (5 to 17) years were evaluated. Prior to inclusion in the study, horses underwent clinical examinations and were determined to be free of lameness. Horses were selected from a pool of horses used for research purposes. Individual housing was provided at a nearby research facility, and all horses were fed a standard pelleted diet and had free access to water.

Nonfocused ESW treatment—All horses were treated with nonfocused ESWs on day 0 of the study. Prior to treatment, horses were sedated with detomidine hydrochloride (0.02 mg/kg, IV) and butorphanol tartrate (0.02 mg/kg, IV). The hair on the palmar aspect of the pastern of both forelimbs was clipped, and after application of a coupling gel, 2,000 pulses were applied over the medial palmar digital nerve of the left forelimb by use of a nonfocused shock wave generator.[a] Shock waves were applied at a frequency of 240 pulses/min, at a machine pressure of 0.25 MPa, and by use of an applicator head 15 mm in diameter. The same treatment was then applied to the lateral palmar digital nerve of the left forelimb. No treatment was applied to the right forelimb. Horses were returned to their stalls, and daily hand-grazing was allowed until subsequent experimental procedures.

Sensory nerve conduction velocity measurements—Three groups of 2 horses each were evaluated 3, 7, and 35 days after ESW treatment, respectively. Horses were sedated with xylazine hydrochloride (0.5 mg/kg, IV) and butorphanol tartrate (0.02 mg/kg, IV), and general anesthesia was induced with ketamine hydrochloride (2 mg/kg, IV) and diazepam (0.15 mg/kg, IV). Horses were positioned in right lateral recumbency, and anesthesia was maintained with isoflurane and oxygen in a semiclosed system. The metacarpophalangeal (pastern) area of both forelimbs were prepared for surgery. A lateral abaxial incision 3 cm long was made along the deep digital flexor tendon in the midpastern area of the left forelimb. The lateral palmar digital nerve was carefully isolated. A second lateral abaxial 1-cm-long incision was made at the level of the lateral proximal sesamoid bone, and the lateral palmar digital nerve was isolated at this site. A pair of sterile needle electrodes was placed directly into the nerve at the distal incision site (stimulating electrodes) and at the proximal incision site (recording electrodes). A ground electrode was placed in the skin of the dorsal surface of the pastern between the stimulating and recording electrodes.[11] The stimulating electrode was activated by a stimulator that was a component of an electromyography system[b] (**Figure 1**). The recording and ground electrodes were connected to the preamplifier of an electromyographic recorder. The distance between stimulating and recording electrodes was measured by use of a sterile measuring tape, and the value was entered into the system computer. Square wave stimuli at 1 Hz and of 100 microsecond's duration were generated by the stimulator at various voltage settings until a visible compound action potential was recorded by the recording electrodes and displayed on the system monitor. Ten responses per nerve were used to calculate mean values by the system computer, and measurements in each nerve were performed in duplicate to evaluate reproducibility. Sensory nerve conduction velocity was calculated by the system computer, and the mean of measurements for each nerve was recorded. Subsequently, the medial palmar digital nerves of the left and right forelimbs were exposed in a similar manner through medial abaxial incisions and SNCV was measured as described.

Palmar digital neurectomy—Immediately after SNCV measurements, a 4-cm-long segment of each palmar digital nerve was resected with a scalpel blade. Representative transverse sections were placed in primary fixative (1.25% glutaraldehyde and 2% formaldehyde in 0.1M cacodylate buffer) overnight for TEM. Incisions were closed with simple interrupted skin sutures with 2-0 nylon suture material,[c] and bandages were applied. After recovery from anesthesia, horses were returned to their stalls. Bandages were applied until suture removal 2 weeks after surgery. No surgical complications were observed.

TEM—Transverse sections (area, 3 mm^2) of excised nerve segments were washed twice in 0.1 mol/L sodium cacodylate that contained 5% (wt/vol) sucrose for 15 minutes

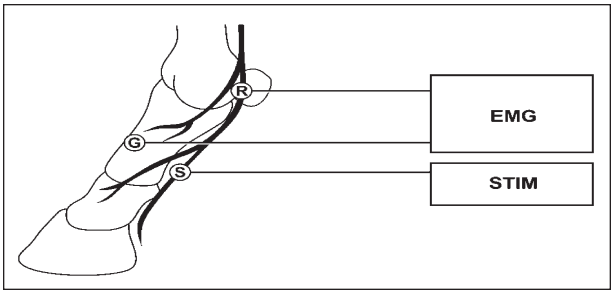

Figure 1—Schematic representation of sites of positioning of electrodes for measurement of sensory nerve conduction velocity in palmar digital nerves of horses treated with nonfocused extracorporeal shock waves. S = Stimulating electrode. R = Recording electrode. G = Ground electrode. EMG = Electromyography system. STIM = Electromyographic stimulator.

ers of the myelin sheath in medium- to large- diameter myelinated axons; however, no changes were observed in small diameter myelinated and nonmyelinated axons. No traumatic or inflammatory changes were found in treated nerves.

Discussion

Our study revealed that a single treatment with nonfocused ESWs over palmar digital nerves resulted in significantly lower SNCVs, compared with control nerves, and in separation and disruption of the layers of the myelin sheath in medium- to large- diameter myelinated axons. A significant proportional difference in SNCV between ESW-treated nerves and control nerves was observed 3 and 7 days after treatment; however, treated medial, but not lateral, nerves had a significantly lower SNCV, compared with control nerves, 35 days after treatment. We believe that the absence of electrophysiologic changes in treated lateral nerves on day 35 is most likely attributable to lack of precision during application of ESWs with the handheld applicator and that the effects of ESW application on conduction in peripheral nerves are likely to last beyond our follow-up period (35 days).

Results of nerve conduction studies closely parallel structural abnormalities of nerves and depend on the type and degree of nerve damage. Partial demyelination and traumatic damage of the myelin sheath of myelinated axons result in impaired saltatory conduction because of an increase in internodal capacitance and conductance.[12] More local current is lost to charge the membrane capacitance and via leakage through the internodal membrane before reaching the next node of Ranvier; therefore, axons with a damaged myelin sheath characteristically have lower conduction velocity and temporal dispersion.[12] Impaired nerve conduction without actual structural damage of the axonal cytoplasm is referred to as neuropraxia and represents the mildest form of peripheral nerve injury.[12] Therefore, our electron microscopic findings could explain the lower SNCV measured in ESW-treated nerves. The lack of electron microscopic changes in nonmyelinated and small-diameter myelinated axons in treated nerves was consistent among horses; we speculate that these structures are either too small or that they provide an insufficient local change in impedance for ESWs to exert their effects.

Treatment of lameness is a challenge for the equine practitioner who wishes to provide pain relief, reinstitute athletic use of the horse, and minimize economic loss while operating within ethical and regulatory constraints of modern competition. This has led to a growing interest in alternative treatments that appear to result in improved and accelerated healing and a shorter convalescence period. Extracorporeal shock wave treatment represents such an alternative and appears to be gaining interest and acceptance among veterinarians, trainers, and owners as a treatment for selected orthopedic injuries in horses.

Shock wave-induced stimulation of bone and soft tissue healing is reported in humans[9,13] and other species[1,14,15]; however, the exact effects of high- pressure waves on tissues are not fully understood. Treatment with focused and nonfocused ESWs also results in a transient analgesic effect that is apparently independent of any other beneficial effect on tissues.[1] The mechanism of this analgesic effect is not known. One investigator suggested 3 hypotheses to explain the mechanism of shock wave-induced analgesia in humans. The first hypothesis is that shock waves induce cell damage; therefore, peripheral nociceptors cannot build up a membrane potential sufficient to transmit pain signals. The second hypothesis is that nociceptors are overstimulated by shock waves and emit high frequency impulses to peripheral nerve fibers, which are suppressed by a gate control mechanism. The third hypothesis is that shock wave-induced pericellular free radicals induce the local release of unknown pain-suppressing substances.[16]

In humans, the analgesic effect after ESW treatment appears to be bimodal. An immediate initial decrease in pain that lasts 3 to 4 days is followed by a recurrence of pain and then a second gradual decrease in pain over the ensuing 3 to 4 weeks.[8] The initial effect is attributed to the direct effects of shock waves on nociceptors and impaired substance P synthesis, whereas the second phase of pain relief is believed to be the result of angiogenesis and tissue matrix remodeling associated with tissue healing.[8] A similar bimodal analgesic response is observed in horses undergoing shock wave treatment.[1,6]

Musculoskeletal activity without full perception of peripheral pain could potentially place equine athletes with preexisting lesions at greater risk of sustaining career-ending or life-threatening injuries that include complete spiraling condylar fracture of the third metacarpal or metatarsal bones after sustaining an incomplete fracture, and breakdown injuries of the suspensory apparatus. This risk has been recognized by the equine industry and strict regulations concerning the use of ESW treatment before competitions have been issued. McClure and Merritt[1] recommend that large nerves, blood vessels, and active growth plates be avoided during ESW treatment in horses. Because of the anatomic proximity of target tissues to these structures, ESW-induced trauma cannot always be avoided; with respect to nerves, occasionally trauma is even desired. In horses, the palmar digital nerves are targeted directly when ESWs are used to treat disorders of the foot, such as navicular disease.[5] To the authors' knowledge, ESW treatment is not used to specifically treat peripheral nerves in humans.

We do not propose a definitive explanation for the analgesic effect observed after ESW treatment in horses; however, our results support the premise that ESWs can cause damage to peripheral nerves that results in slower conduction velocities and potentially impaired perception of peripheral pain.

Morphologic and functional changes associated with neuropraxia are reversible over time.[17] Repeated application of ESWs, however, may cause more extensive damage to exposed peripheral nerves and may result in prolonged or permanent alterations in nerve conduction. Renal damage after ESW treatment of

and postfixed in 1% OsO_4 in distilled water for 1 hour. After several washes in distilled water, nerve sections were stained with 0.5% (wt/vol) uranyl acetate in distilled water overnight. Nerve sections were dehydrated in graded ethanol solutions of increasing concentration (30%, 50%, 70%, 95%, and 100%), infiltrated with embedding medium,[d] and polymerized. Polymerized blocks were cut into sections 0.1 µm thick by use of an ultramicrotome. Sections were stained with uranyl acetate and lead citrate and examined by use of a transmission electron microscope.[e] The investigator (WGH) was unaware of treatment status of each nerve.

Statistical analyses—Sensory nerve conduction velocities were considered continuous, and the proportional difference in SNCV for treated lateral and medial nerves, compared with control nerves, within each horse, was analyzed by use of a mixed-effect linear model that accounted for random variance of horse and limb, nested within time points. Ad hoc comparisons were made within each nerve and across treated nerves at each time point, maintaining type I error at 0.05. A software program[f] was used for the analysis.

Table 1—Mean (individual values) sensory nerve conduction velocities (SNCV [m/s]) in palmar digital nerves of horses, 3, 7, and 35 days after treatment with nonfocused extracorporeal shock waves.

	Day		
Nerve	**3**	**7**	**35**
LL	32.45* (32.7, 32.2)	37.0* (39.1, 34.9)	51.95 (61.7, 42.2)
LM	32.15* (34.9, 30.4)	32.26* (34.9, 30.4)	37.9* (37.4, 38.4)
RM	48.2 (49.9, 46.5)	60.25 (61.1, 59.4)	43.35 (44.7, 42.0)

*Significantly lower, compared with control (RM).

LL = Left lateral palmar digital nerve (treated). LM = Left medial palmar digital nerve (treated). RM = Right medial palmar digital nerve (control).

No significant ($P < 0.05$) differences in SNCV between LL and LM nerves on days 3 and 7 were found.

Results

SNCVs—Velocities in treated and control nerves were determined for each horse (**Table 1**). Careful surgical exploration and identification of palmar digital nerves prior to needle placement resulted in reliable and reproducible SNCV measurements. All nerves treated with nonfocused ESWs had significantly lower SNCVs, compared with control nerves, on days 3 and 7. Significantly lower SNCVs in treated medial but not lateral nerves, compared with control nerves, were found on day 35. There was no significant difference in SNCV between treated medial and lateral nerves on days 3 and 7.

TEM—Transmission electron photomicrographs of transverse sections of treated and control nerve segments were examined (**Figure 2**). Medium- to large- (5 to 15 µm) and small- (1 to 5 µm) diameter myelinated axons were observed. Nonmyelinated axons (0.5 to 2 µm in diameter) were surrounded by Schwann cells and embedded in loose collagenous endoneurium. In control nerves, uniform concentric layers of myelin in myelin sheaths were evident in medium- to large- and small- diameter myelinated axons, and no traumatic or inflammatory changes were observed. Transmission electron photomicrographs of sections of treated nerves 3, 7, and 35 days after ESW treatment, revealed extensive separation and disruption of the lay-

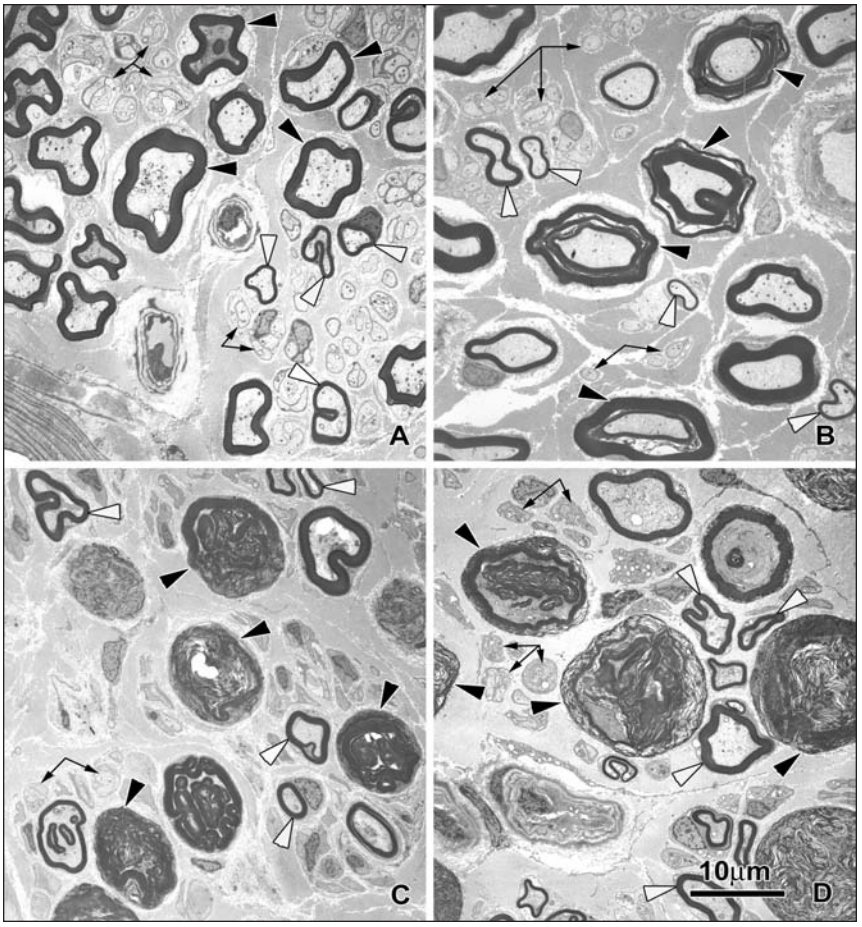

Figure 2—Transmission electron photomicrographs of transverse sections of nontreated palmar digital nerves A—and palmar digital nerves treated with nonfocused extracorporeal shock waves (B, C, and D) in horses. (A) Medium- to large- (black arrowheads) and small = diameter (white arrowheads) myelinated axons and numerous nonmyelinated axons (black arrows) are evident. B—Left medial palmar digital nerve 3 days after treatment. Notice the separation of layers of myelin in medium- to large- diameter myelinated axons. No changes are evident in small diameter myelinated axons and nonmyelinated axons. C—Left medial palmar digital nerve 7 days after treatment. Severe myelin sheath disruption is evident in medium to large diameter myelinated axons. No changes are evident in small - diameter myelinated and nonmyelinated axons. D—Left medial palmar digital nerve 35 days after treatment. Medium- to large- diameter myelinated axons reveal similar changes as in (C). No changes are evident in small = diameter myelinated axons and nonmyelinated axons. Uranyl acetate and lead citrate stain; bar = 10 µm.

nephroliths in dogs is cumulative depending on dose (voltage and number of shock waves) and frequency (number of shock waves/s) of shock waves.[18,19] Results of a study conducted in rabbits also revealed dose-dependent morphologic damage in the gastrocnemius tendon after application of ESWs.[20] We speculate that application of a higher total dose of ESWs would result in prolonged duration of impaired nerve conduction and more extensive morphologic damage of treated peripheral nerves. The duration of morphologic nerve damage and impaired nerve conduction was not assessed beyond 35 days in our study. Our results indicate that further research would be necessary to assess the effects of nonfocused ESWs on peripheral nerves after a longer time period and after multiple treatments.

Although the small sample size of our study limits our ability to draw strong conclusions and despite the fact that our findings do not provide a conclusive explanation for the analgesic effect observed clinically, we recommend cautious use of ESW treatment in equine athletes before training or competition.

[a]Swiss DolorClast Vet, EMS Electro Medical Systems, Nyon, Switzerland.
[b]Cadwell Sierra EMG/EP, Cadwell Laboratories, Kennewick, Wash.
[c]Ethicon, Johnson & Johnson, Somerville, NJ.
[d]Poly/Bed 812, Polysciences Inc, Warrington, Pa.
[e]Zeiss (LEO) EM-10C, Carl Zeiss GmbH, Oberkochen, Germany.
[f]PROC MIXED, SAS version 8.0, SAS Institute Inc, Cary, NC.
[g]Ogden JA, Ogden DA. Electrohydraulic SWT: bimodal response (abstr), in *Proceedings*. 5th Cong Int Soc Musculoskeletal Shockwave Ther 2002;21.

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