DOI: 10.1111/papr.13237

RESEARCH ARTICLE

Shock waves as treatment of mouse myofascial trigger points

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Abstract

Introduction: An abnormal increase in spontaneous neurotransmission can induce subsynaptic knots in the myocyte called myofascial trigger points. The treatment of choice is to destroy these trigger points by inserting needles. However, 10% of the population has a phobia of needles, blood, or injuries. Therefore, the objective of this study is to verify the usefulness of shock waves in the treatment of myofascial trigger points.

Methods: Two groups of mice have been developed for this: healthy muscles treated with shock waves; trigger points affected muscles artificially generated with neostigmine and subsequently treated with shock waves. Muscles were stained with methylene blue, PAS-Alcian Blue, and labeling the axons with fluorescein and the acetylcholine receptors with rhodamine. Using intracellular recording the frequency of miniature endplate potentials (mEPPs) was recorded and endplate noise was recorded with electromyography.

Results: No healthy muscles treated with shock waves showed injury. Twitch knots in mice previously treated with neostigmine disappeared after shock wave treatment. Several motor axonal branches were retracted. On the other hand, shock wave treatment reduces the frequency of mEPPs and the number of areas with endplate noise.

Discussion: Shock waves seem to be a suitable treatment for myofascial trigger points. In the present study, with a single session of shock waves, very relevant results have been obtained, both functional (normalization of spontaneous neurotransmission) and morphological (disappearance of myofascial trigger points). Patients with a phobia of needles, blood, or injuries who cannot benefit from dry needling may turn to noninvasive radial shock wave treatment.

KEYWORDS
myofascial pain syndrome, myofascial trigger point, neostigmine, shock waves

INTRODUCTION

The most frequent cause of muscular pain is myofascial pain syndrome[1] (MPS). This syndrome is a collection of signs and symptoms caused by the presence of myofascial trigger points (MTrPs).[2] MTrPs are painful palpable nodules that increase their pain with active stretching and contraction.[2]

Myofascial trigger points can be treated conservatively or invasively.[2] Invasive treatment, called "dry needling", consists of introducing an acupuncture-like needle to reach the trigger point in order to destroy it.[3] Alternatively, the galvanic current can cross through the needle with similar results.[4] Conservative treatment (without needles) consists of manual therapy techniques or lasers.[5] Dayanır et al.,[6] working on non-specific chronic low back pain, described that the clinical effectiveness of several manual therapy techniques (manual pressure release, counter-exertion, and integrated neuromuscular inhibition technique) indicated that they might provide a slightly greater improvement in pain during activity, MTrP deactivation, and pain-related disability. The ischemic compression is characterized by continuous compression or sustained pressure multiple times at the trigger point or approximate regions, frequently lasting 30 to 90 seconds.[7] This conservative treatment has been controversial MTrPs. For example, a few years ago a review including relevant randomized controlled trials up to 2013 showed moderate evidence that ischemic compression had a beneficial effect on MPS.[8] More recently, however, the use of ischemic compression alone was reported to improve pain tolerance in MPS subjects compared with an inactive control.[9] There are intermediate options between invasive and non-invasive physiotherapy since instrumented manual compression would provide a closer approach to the current options used by therapists since the effort required to treat MTrPs is high for them and this type is sometimes preferred for treatment.[10]

In general, the invasive treatment produces good results with few recurrences.[11,12] Moreover, dry needling should be considered the first-choice treatment to reduce MTrP pain in the short term.[13] However, there are patients with extreme fear, uncontrollable, and irrational fear of needles (belonephobia) representing 10% of the world population.[14,15] Moreover, 20%–50% of adolescents and 20%–30% of young adults are afraid of needles.[14] Thus, extracorporeal shock waves therapy, specifically radial extracorporeal shock waves therapy, is an alternative treatment for all those patients.[16–18]

Radial shock waves are generated mechanically: a pneumatic projectile strikes a transmitter inside an applicator.[19] By keeping the device in contact with the skin using ultrasound gel, the shock waves spread radially toward the underlying tissues. This non-invasive therapy is effective, fast, and inexpensive in the treatment of a variety of musculoskeletal conditions.[16–18,20,21] Shock waves promote angiogenesis, increase perfusion, and alter pain signaling in ischemic tissues caused by calcium influx.[20,22] Chronic pain is also relieved by shock waves, both by partial selective denervation of unmyelinated nerve fibres[23] and by degeneration of free nerve endings.[24] Furthermore, at high intensities, shock waves promote the elimination of acetylcholine receptors at the neuromuscular junction or even the destruction of the motor endplate.[25,26] Currently, the most accepted theory about the pathophysiology of MTrPs involves an increased release of the neurotransmitter acetylcholine, ACh.[19,27,28] Thereafter, these nervous consequences described can be beneficial for the treatment of MTrPs.

In the present work, we evaluate the efficacy of radial shock waves in the treatment of MTrPs.

MATERIALS AND METHODS

Animals

The mice were cared for in accordance with the guidelines of the European Community's Council Directive (2010/63/EU) and the Spanish Royal Decree 53/2013 for the humane treatment of laboratory animals. Animal Research Committee of Spain (Reference number: 0233) reviewed and approved all experiments on animals. The experiments were performed on young adult Swiss male mice (seventy-two 50 days post-natal animals; Charles River). Mice were habituated to the facility for at least 1 week prior to studies and were housed in groups of four, with sawdust bedding, and ad libitum access to water and food throughout. The animals' rooms were maintained at a temperature of 22 ± 2°C, a relative humidity of 50 ± 10%, and a 12 h light/dark automatic light cycle. Animals were deeply anesthetized with isoflurane (Vetpharma) before being euthanized by exsanguination. Table 1 shows the techniques, periods, and muscles used.

TABLE 1 Methodological approach.

		Functional approach		Morphological approach		
Muscle	**Group**	**Intracellular recordings**	**EMG**	**Methylene blue**	**PAS-Alcian Blue**	**Immunohistochemistry**
LAL	Control	■				■
	ShW	■		■		■
	NTG	■			■	
	NTG + ShW	■			■	
Gastrocnemius	Control		■			
	ShW		■			
	NTG		■			
	NTG + ShW		■			

Abbreviations: EMG, electromyography; LAL, *leavor auris longus*; NTG, neostigmine; ShW, shock waves.

Anticholinesterase exposure

Neostigmine methyl sulfate (NTG; Sigma; 0.1 mg NTG/kg bw) was injected subcutaneously and, to ensure the correct drug administration, a cholinergic syndrome should appear within half an hour post-treatment (for a complete description and further details see Margalef et al.[27]).

Radial shock waves

A generator of radial shock waves (Physiogold50®MTS) was used. The doses used consist of a frequency of 4 Hz, 300 pulses in continuous mode, and an intensity of 0.16 MPa for the *levator auris longus* muscle (LAL) muscle and 0.30 MPa for the gastrocnemius. The shock waves were administered to the deeply anesthetized mice.

We used LAL muscles for morphological and electrophysiological studies and gastrocnemius muscles for electromyography. Shock waves were applied 30 min after injecting neostigmine to control animals.

Histological techniques

Methylene blue

In order to rule out the idea that radial shock waves can cause cell damage, that staining was performed. Whole LAL muscles were removed and exposed to a 1% methylene blue (Sigma-Aldrich; Ref: 03978) in 1% borax (2 min; Sigma-Aldrich; Ref: 221732). This technique was used after 30 min and 24 h of applying the shock waves. Three animals were selected per experimental group.

PAS-Alcian Blue staining

The LAL muscles were not fixed and were directly labeled. In this manner, the cellular membrane is quite preserved and the extracellular glycosaminoglycans (GAGs) are better labeled. For a complete description and further details see Margalef et al.[27] Shock waves were applied 30 min after injecting the neostigmine. PAS-Alcian was evaluated 30 min after neostigmine treatment and immediately after shock wave application. Three animals were selected per experimental group.

Immunohistochemistry

This technique allows the identification of both pre and postsynaptic components. Whole LAL muscles were removed and fixed in 4% paraformaldehyde in phosphate-buffered saline. The LALs were labeled for postsynaptic nicotinic acetylcholine receptors with tetramethyl rhodamine isothiocyanate (TRITC-α-BTX). Axons were identified with anti-neurofilament 200 kDa conjugated to fluorescein (green emission). Immunohistochemistry was carried out 3 h after applying the shock waves. Immunohistochemistry was evaluated in healthy muscles immediately after the application of shock waves. Five animals were selected per experimental group.

Morphometry

Samples were observed with a Nikon Eclipse TE2000-U fluorescence microscope. Neuromuscular junctions with retracted presynaptic branches were identified and counted. The retracted branches were thicker than the normal unaffected branches (Figure 1A). The data were expressed as a percentage of synapses having retracted branches with respect to the total number of synapses.

The Digimizer image analysis software (https://www.digimizer.com/) was used to perform morphometry. The postsynaptic area, the total length of the presynaptic component, and the number of axonal branches of the latter were analyzed. The opposition index and the presynaptic length-postsynaptic area relationship were also calculated to check whether the presynaptic component continued to overlap the entire postsynaptic component. (Figure 1B). The samples were evaluated 3 h after treatment with shock waves to enable cellular reactions to take place.

Intracellular recordings

In order to assess whether shock waves have a physiological significance in neurotransmission mEPPs were recorded. The LAL muscle was dissected, and spontaneous miniature endplate potentials (mEPPs) were recorded intracellularly. The mEPP frequency was recorded for 100 s from at least 15 different neuromuscular junctions and the mean values were determined. The mean amplitude (mV) per fiber was calculated and corrected for nonlinear summation,[29] assuming a membrane potential of −80 mV.

Recording of mEPPs was performed on healthy control muscles, shock waves treated healthy muscles, and shock waves applied 3 h after treatment with neostigmine (MTrPs model). Five animals were used per group. To optimize the animals, after performing EMG records in the gastrocnemius muscles, intracellular records of the LAL muscles of each animal were made.

Electromyography

Spontaneous neurotransmission from the neuromuscular junction can be recorded as “endplate noise”.[27,30]

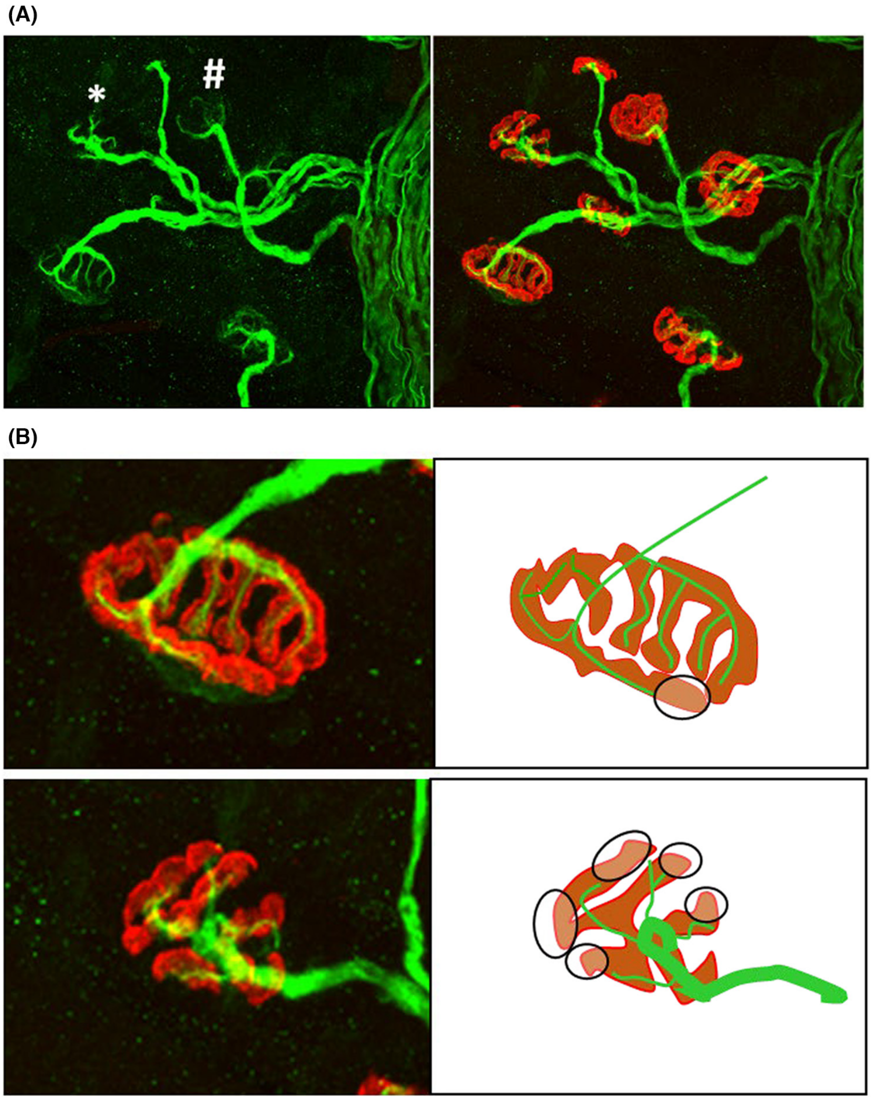

FIGURE 1 Immunohistochemistry. (A left) The axonal ramifications of the presynaptic component are shown. Note that in normal synapses (#) all the branches are very thin, but in the synapses with retractions (*), some branches are unusually thick. (A right) The presynaptic components are shown with their corresponding postsynaptic components. Note that the appearances of the postsynaptic components under the branches in retraction are not different from those of normal synapses. Initial magnification 200×. (B) Two examples of lack of apposition between the axonal presynaptic component (green) and the postsynaptic component (red). On the right, there is a scheme to better illustrate this situation with circles. In control muscles, the situation shown in the upper image can be found. The example is shown at the bottom, and more postsynaptic areas without axon has only been obtained in muscles treated with shock waves. This study was carried out 3 h after applying the shock waves.

Thus, to reinforce the results obtained using the ex vivo intracellular model, in vivo, recordings were performed by electromyography in gastrocnemius muscles. Recordings were obtained from an anesthetized animal at a controlled room temperature (22–25.8°C). The muscle used for this study was the gastrocnemius because of its ease of access and suitability. Recordings were obtained with an electromyography system (MedelecMystro plus, GR20) using a monopolar EMG needle (Natus Manufacturing Limited). For a complete description and further details see Margalef et al.[27] The number of areas with endplate noise (maximum 12) and the frequency (number of potentials per second that appeared, expressed in Hz) was recorded.

Thirty minutes after injecting the neostigmine, the right legs were treated with shock waves, then and the right legs (experiment) and the left legs (control) were recorded 3, 12, and 24 h later. Five animals were used in each group. To optimize animals, after the EMG recordings of the 3 h group, intracellular recordings of their LAL muscles were made.

Statistical procedure

Values are expressed as means ± SEM. The values are expressed as "Percentage of change". This is defined as [experimental value/control value] × 100. We used the two-tailed Welch's *t*-test for unpaired values because our variances were not equal. We prefer this test because it is more conservative than the ordinary *t*-test. Differences were considered significant at $p < 0.05$.

RESULTS

Methylene blue

After 30 min of applying the shock waves, the muscular fibers remained normal and unchanged (Figure 2A) suggesting that there are no injuries caused by short-term shock waves. Moreover, 24 h after, no inflammatory cells can be seen (Figure 2B).

PAS Alcian

The contraction knots are the morphological evidence of the MTrPs. Thirty minutes after the injection of NTG, several contraction knots can be seen surrounding intramuscular nerves (Figure 3A; see also Margalef et al.[27]). As shown in Figure 3B, 3 h after shock wave application, the contraction knots have completely disappeared.

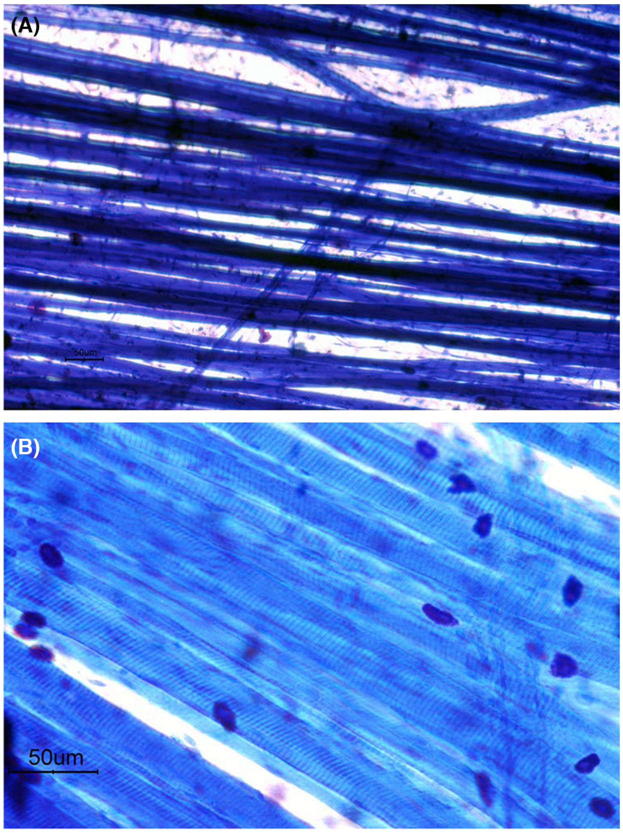

FIGURE 2 Methylene blue. In (A) 30 min after shock wave application, no changes in the muscle were observed. In (B) 24 h after the application of the shock wave, there are no changes in the muscle and any inflammatory dell can be seen. The darkest round structures are the most common mast cells of the *levator auris longus* muscle. Bar: 50 μm.

Immunohistochemistry

Axonal retraction can be identified in some neuromuscular junctions of muscles treated with shock waves. In Figure 1, thin nerve branches that correspond to normal, unaltered branches can be seen (Figure 1A, left). They coexist with other wider and thicker branches clearly showing an altered morphology (Figure 1A, left).

The postsynaptic components have a normal, complete morphological appearance, and no structural modification in any case. The total area of each postsynaptic component was calculated, and no differences were observed with the controls (Figure 4A). These results

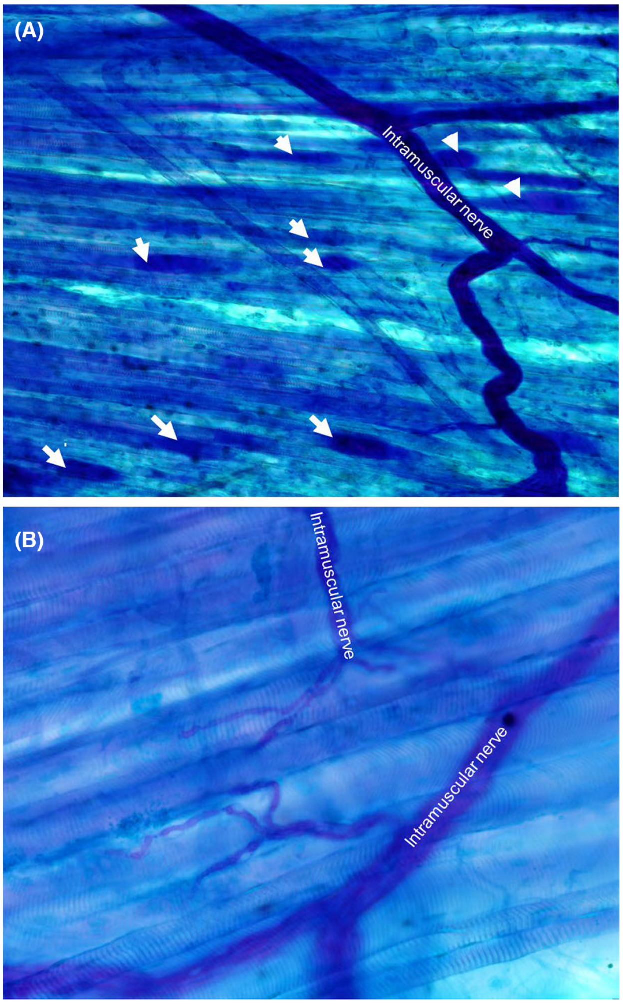

FIGURE 3 PAS/Alcian Blue. In (A) 30 min after injecting neostigmine and before applying shock waves. Contraction knots are observed near intramuscular nerves (arrowheads). In (B) the sample is extracted 3 h after applying shock waves in muscles treated with neostigmine. Note how contraction knots have disappeared. Initial magnification of the two images: 200×.

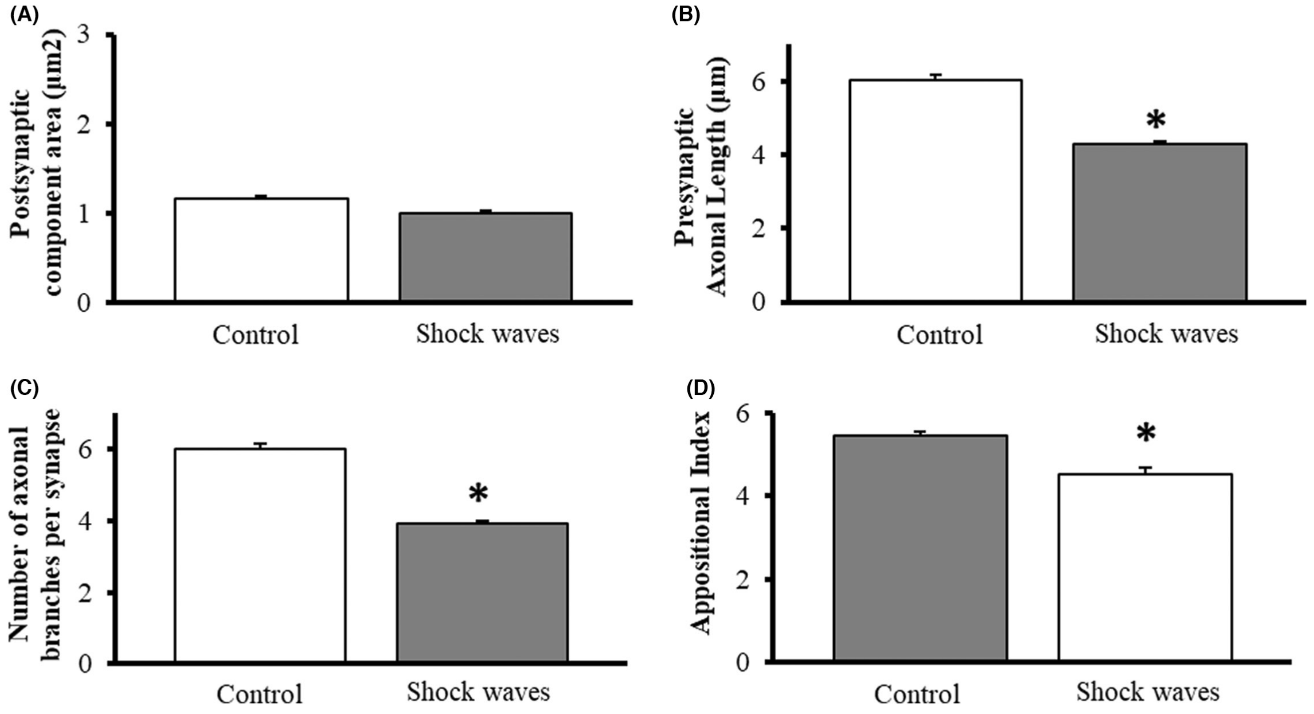

FIGURE 4 Morphometric study. With the immunohistochemical technique, an axonal retraction of some synapses in the muscles treated with shock waves can be observed. In order to analyze this, a morphometric study was performed. (A) Shock waves do not affect the aggregation of postsynaptic receptors. (B) The total length of presynaptic axons was determined and decreased with shock waves. (C) Some axonal branches have completely disappeared. (D) Appositional index (Axonal length/postsynaptic area) decreases in the terminals treated with shock waves. $*p<0.05$, $n=225$ synapses from five animals per group.

suggest that shock waves do not affect the aggregation of postsynaptic receptors. To measure axonal involvement at the neuromuscular junction, the total length of the presynaptic axons was calculated. The length of the presynaptic axons of the treated animals was shorter than the controls (Figure 4B). Furthermore, some axonal branches completely disappeared in the treated muscles (Figure 4C).

To assess whether the postsynaptic components were abandoned by their axons as result from an action of shock waves, an "apposition index" was obtained: the ratio of component postsynaptic covered by its axon (Figure 1B). As shown in Figure 4D, the apposition index decreases significantly in shock wave-treated terminals. This result confirms that some postsynaptic components were abandoned by axons in retraction after shock wave treatment.

Intracellular recordings

Miniature endplate potentials were recorded in the LAL muscles 3 h after treatment. The frequency of mEPPs decreased by 30% in control muscles (Figure 5A). In muscles with MTrPs, the frequency of mEPPs is very high (Number of events per minute: 150.7 ± 18.5) and shock wave treatment was able to reverse this situation (Number of events per minute in control: 47.7 ± 5.3: Number of events per minute after applying shock waves to muscles treated with neostigmine: 45.50 ± 4.0; Figure 5A). The amplitude of the mEPPs was not modified by shock waves nor were they increased in the control muscles nor those treated with neostigmine (% of decrease: 7.45, $p<0.05$; Figure 5B). This indicates that the shock probes did not alter the postsynaptic receptors and confirm the observations made in the morphometric set and the morphological images.

Endplate noise recordings

When applied to healthy muscles, shock wave treatment does not affect endplate noise in any area of the muscle (Figure 6). In MTrP animals, the number of areas with recorded endplate noise increases significantly (recorded 3, 12, and 24 h after NTG injection; Figure 6). Interestingly, when the radial shock wave treatment was administered to mice with MTrP previously induced by NTG, the end plate noise recordings were reversed to control values (Figure 6).

DISCUSSION

The present study was designed and conducted to analyze and validate the effect of radial shock wave treatment on MTrP in an animal model. The results demonstrate that the radial shock wave treatment does not affect the muscle fibers morphologically and reverses the contraction knots created in the mouse model muscles. In addition, spontaneous neurotransmission at the neuromuscular junction returns to normal control values.

In the present study, methylene blue staining showed that degenerative histological changes do not appear in muscle fibers after treatment with radial shock waves. However, inflammatory reactions have been reported after 48 h of administration of focal shock waves in rat muscles[15] or even destruction of muscle fibers.[31] The intensity of the shock waves may explain these differences since the inflammatory reaction occurred at a density of 0.16 mJ/mm^2 with 500 impulses, much higher than that used in the present study (300 impulses continuously for a total intensity of 0.16 joules), for a dose of therapeutic use.[15] Therefore, at standard therapy levels, radial shock waves do not cause muscle injury.

The development of validated pharmacologically induced models of MTrPs in mice, by inhibiting acetylcholinesterase activity,[27] allows us to describe the effect of radial shock waves on pathognomonic contraction knots formed near intramuscular nerves. The morphological findings of our experiments clearly show that the MTrPs induced by NTG can be reversed by the application of radial shock waves. A possible dismantling and disorganization mechanism of actin and myosin filaments by focal shock waves has been described.[32] Images of methylene blue-stained muscles do not appear to show disassembled sarcomeres. Another possible mechanism could involve synaptic contacts. Treated muscles with shock waves showed axonal retraction at the level of the neuromuscular junction as previously described in other model.[23,24] Furthermore, the shock

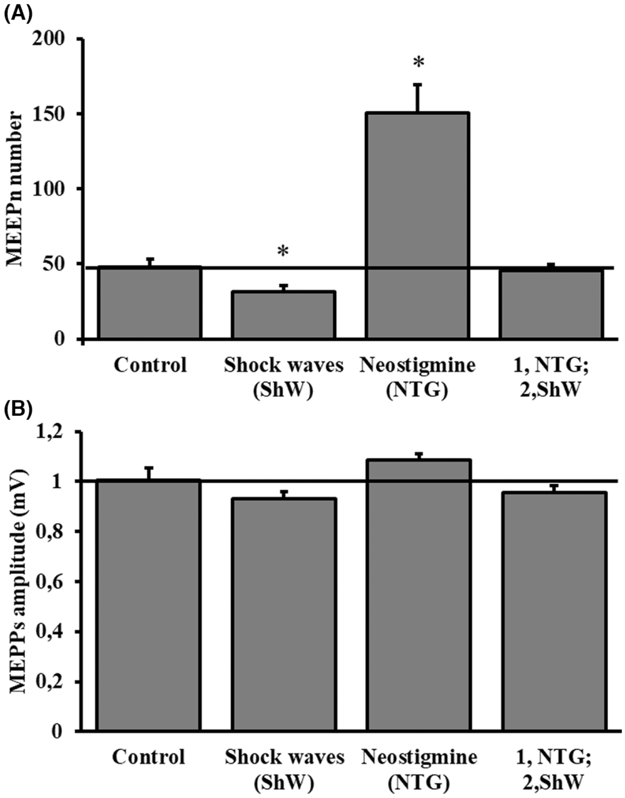

FIGURE 5 Intracellular recordings. (A) The number of miniature endplate potentials (mEPPs) per second. Note that the significant increase in mEPPs frequency in neostigmine-treated muscles (over 370% more than in control) was reversed by shock waves. (B) The amplitude of mEPPs expressed in mV. Shock waves (ShW) decrease the mEPPS frequency without affecting their size. Animals treated with neostigmine (NTG) show a significant increase in the mEPPS frequency that was reversed by the action of shock waves (1, NTG; 2, ShW). The continuous line refers to the control values. *$p<0.05$. $N=95$ synapses from five animals per column.

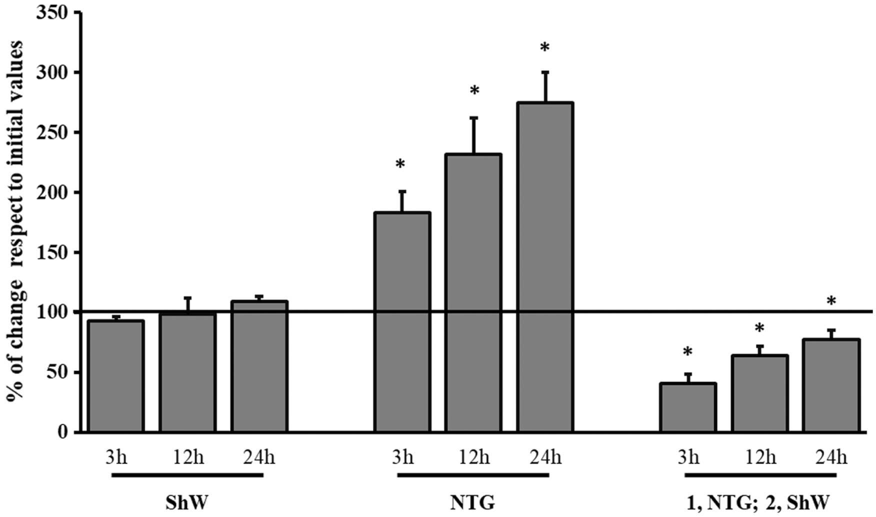

FIGURE 6 Endplate noise recordings. The application of shock waves (ShW) in healthy muscles practically does not have modifications. Subcutaneous neostigmine (NTG) was injected in other animals and the recording was performed at 3, 12, and 24 h. Note that a significant increase in the number of areas with end plate noise was obtained. Finally, in neostigmine-treated animals shock waves were applied after 3, 12, and 24 h (1, NTG; 2, ShW). In this case, the numbers are expressed in % of the data of the animals treated with neostigmine. The shock waves completely reversed the action of neostigmine. *$p<0.05$. $N=5$ animals per column.

wave-treated preparations showed a decrease in the total length of the presynaptic elements and a reduction in the apposition index between the presynaptic and postsynaptic elements. This effect could mean reduced neurotransmission leading to the disappearance of an MTrP. Kenmoku and collaborators have described other intense effects on the postsynaptic component of the neuromuscular junction after the application of shock waves that include the elimination of acetylcholine receptors and the destruction of the motor endplate terminal.[25,26] Although Kenmoku et al. also used radial shock waves, as in the present study, it was observed that they had higher impulses (2000) than those used in this study (300), which justifies their more intense effects. According to the results obtained in the present study, the postsynaptic component is not implicated in the modification of the neurotransmission. Interestingly, no variation in the amplitude of such mEPPs occurred, which confirms that there is no participation of the postsynaptic component. As shown in the immunofluorescence images, the reduction in the frequency of mEPPs seems to correlate well with a diminished number of axonal branches. That is, shock waves completely reverse spontaneous neurotransmission, which reverses MTrPs.

The intracellular recording obtained a decrease in the frequency of mEPPs in healthy muscles treated with shock waves. This result is consistent with the morphometric study performed, whereby fewer axonal branches were available to release ACh. However, the electromyographic recordings did not show changes in the plaque noise of healthy muscles treated with shock waves. This is because the intracellular recording technique is much more sensitive than electromyography. From the clinical point of view, there are no references indicating that radial shock waves have any negative consequences on healthy muscles. The reduction in the frequency of mEPPs obtained in this study has no clinical translation. mEPPs correspond to the release of acetylcholine (ACh) in an insufficient amount to cause an action potential or muscle contraction.[33] On the other hand, if this reduction in the frequency of the mEPPs means a loss of an axonal branch and, therefore, globally, a reduction of the volume of ACh released in the evoked neurotransmission, this does not affect the contraction either. The evoked neurotransmission works with certain safety margins are very large so only very large reductions in ACh release can mean contraction failure.[33]

Kenmoku's team also obtained a reduction in the amplitude of the action potential in muscles exposed to radial shock waves.[26] The results of electromyography are consistent with those obtained with intracellular recordings.

In the animal model of MTrPs, the increase in endplate noise due to the action of neostigmine is consistent with the increase in the effects of acetylcholine since neostigmine inhibits the action of acetylcholinesterase.[27] After applying shock waves, the noise areas at the end plate decrease significantly. The studies carried out by Kimura showed that the recording of spontaneous electrical activity is closely related to obtaining endplate noise,[32] so these results complement the previous ones of intracellular recording, confirming the hypothesis of axonal retraction.

Dry needling is one of the most effective ways to treat MPS. Every year new articles appear that demonstrate its effectiveness.[34] The needle introduced into the trigger point injures the muscle area with MTrPs in addition to partially denervating it.[35] This DN-induced denervation is similar to that obtained in this study with shock waves. In clinical practice, extracorporeal shock wave therapy is currently used successfully in the treatment of MTrPs. For example, Luan et al.[16] reported that extracorporeal shock wave therapy was as effective as dry needling in relieving pain, improving function, and reducing shear modulus in patients with myofascial trigger points after a series of three treatments. Furthermore, Hong et al.[36] found that extracorporeal shock wave therapy for myofascial pain reduced pain better compared to the injection of anesthetics in MTrPs. Gezginaslan and Gümüş-Atalayconducted a prospective, randomized, single-blind clinical study comparing a group treated with high energy flux density extracorporeal shock wave with another group in which non-invasive physiotherapy techniques (superficial hot pack, TENS, and ultrasound).[37] These authors found shock waves to be more effective for pain, quality of life, sleep, fatigue, depression, and disability in patients with MPS than noninvasive physiotherapy techniques. A factor that can be decisive in the treatment of ischemic pressure is the physiotherapist's fatigue when applying pressure, decreasing the pressure over time. This could be remedied with the use of instrumented compression techniques.[10]

The mechanism of action of the different treatments that are applied to trigger points is usually little known. As mentioned above, it seems clear that dry needling eliminates trigger points.[35] The use of electrical currents seems to return the frequency of mEPPs to control values.[27] The biological repercussions of manual therapy have not been adequately evaluated. However, the biological effects of shock waves have been relatively better studied: dismantling and disorganization mechanism of actin and myosin filaments,[32] axonal retraction at the level of the neuromuscular junction,[23,24] the elimination of acetylcholine receptors and the destruction of the engine endplate terminal.[25,26] In the present study we found that the radial shock waves return to normal the frequency of the mEPPs due to axonal retraction.

CONCLUSION

Radial shock waves are harmless and completely dissolve the characteristic contraction knots of MTrP.

There is axonal retraction at some neuromuscular junctions of the shock wave-treated muscles without affecting postsynaptic receptor aggregation. Taken together, this causes spontaneous neurotransmission to return to control values. The present study provides biological insights into why radial shock waves may be effective in treating MTrPs. Finally, patients with a phobia of needles, blood, or injuries who cannot benefit from invasive physical therapy may turn to noninvasive radial shock wave therapy.

ACKNOWLEDGMENTS

Singular thanks to the MTS Company, especially to Mr. Alejo Leopard for unconditionally contributing the Physio Gold 50 shock waves equipment for the realization of this study.

FUNDING INFORMATION

The authors received no specific funding for this work.

CONFLICT OF INTEREST STATEMENT

The financial interests of the authors in the context of this work have been disclosed. None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data is available in an excel file Data S1 attached as complementary information.

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SUPPORTING INFORMATION

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

Data S1

How to cite this article: Monclús P, Bosque M, Margalef R, Colomina MT, Valderrama-Canales FJ, Just L, et al. Shock waves as treatment of mouse myofascial trigger points. Pain Pract. 2023;23:724–733. https://doi.org/10.1111/papr.13237