Effect of radial shock wave therapy on pain and muscle hypertonia: a double blind study in patients with multiple sclerosis

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Abstract

Background: Radial shock wave therapy (RSWT) has been extensively used in rehabilitative medicine to treat pain and, more recently, muscle hypertonia in patients with cerebral palsy and stroke.

Objectives: To assess long-term effects of RSWT in a cohort of subjects affected by multiple sclerosis suffering from painful hypertonia of ankle extensor muscles.

Methods: In this randomised, double blind, placebo controlled study, 34 patients were treated with 4 sessions of RSWT (once weekly) and 34 patients were treated with placebo. Participants were assessed at baseline, one week after the first session, one week and 4 weeks after the last session. Pain was measured using the visual analogue scale for pain, while muscle tone was assessed using the modified Ashworth scale. Spinal excitability was evaluated using the H-reflex.

Results: After RSWT, muscle tone was decreased one week after the last session and pain was decreased at all follow-up evaluations, while spinal excitability was unaffected. No significant changes were found after the placebo treatment.

Conclusions: RSWT can reduce pain and muscle tone in MS patients without adverse effects. The lack of RSWT effects on spinal excitability supports the idea that RSWT is likely to act on non-reflex hypertonia, for example reducing muscle fibrosis.

Introduction

Spasticity, which can be defined as a form of hypertonia due to a velocity-dependent increase in tonic stretch reflexes resulting from abnormal spinal processing of proprioceptive inputs[1], is one of the clinical sign of upper motor neuron (UMN) syndrome. In addition to reflex hypertonia, however, patients with UMN syndrome are also suffering from a non-reflex hypertonia, due to connective tissue changes[2].

Since the late 1980s, Extracorporeal Shock Wave Therapy (ESWT) has been widely and successfully used in the treatment of pain in various musculoskeletal disorders[3]. Moreover, ESWT has been successfully used for the treatment of hypertonia in subjects with UMN syndrome[4,5]. ESWT devices use pressure waves generated through electromagnetic, electro-hydraulic and piezoelectric sources. These waves have the point of higher pressure at the centre of their focus which is placed within the treated tissue; thus they are defined as focused shock waves[6,7].

In 1999, a new technology using a ballistic source to generate pressure waves was introduced. This technology is called Radial Shock Wave Therapy (RSWT). The ballistic source consists of a tube within which compressed air (1-4 bar) is used to fire a bullet that strikes a metal applicator placed on the patient's skin. The applicator transforms the kinetic energy of the bullet into radially expanding pressure waves with a low penetration power (less than 3 cm). These unfocused shock waves have their point of highest pressure at the tip of the applicator, outside the treated tissue[6,7].

It has been shown that both focused (ESWT) and unfocused (RSWT) shock waves produce cavitation bubbles in the treated tissue. The cavitation is consequent to the negative phase of the wave propagation. The rapid collapse of the cavitation bubbles leads to secondary pressure waves. Cavitation-mediated mechanisms could have a central role in the action of both ESWT and RSWT[7].

RSWT has been extensively used in rehabilitative medicine to treat painful musculoskeletal disorders such as medial tibial stress syndrome[8], lateral epicondylitis[9] and plantar fasciitis[10]. Three

recent works suggested that RSWT can reduce hypertonia in patients with UMN syndrome due to cerebral palsy[11,12] and stroke[13]. This clinical improvement has been related to a direct effect of RSWT on muscle fibrosis and other components of non-reflex hypertonia [11].

Muscle hypertonia affects up to 80% of subjects with multiple sclerosis (MS) and is often painful[14]. Pain probably reflects the prolonged abnormal contractions due to spasticity, but it also depends on the musculoskeletal consequences due to spasticity and the other components of the UMN syndrome[1]. The relationship between spasticity and pain is made even closer by the fact that pain increases spasticity, creating a spiralling course of more pain and disability[15].

In the hope to combine the two effects of RSWT on pain and hypertonia, in the present study RSWT was used to treat the painful hypertonia of ankle extensor muscles (triceps surae) in a cohort of subjects affected by MS. The first aim of the study was to assess the clinical effect of RSWT on pain (primary outcome) and hypertonia (secondary outcome) in a randomised placebo controlled parallel arm trial. The second aim was to investigate the mechanisms by which RSWT exert its effects. In order to differentiate the possible effects of RSWT on reflex and non-reflex components of hypertonia, we assessed spinal excitability using H-reflex studies.

Materials and methods

Inclusion criteria

Patients were enrolled at the Department of Neurology, University of Genoa, according to the following criteria: 1) MS diagnosed according to revised McDonald's criteria[16] with a Kurtzke Expanded Disability Status Score (EDSS) >4; 2) hypertonia of ankle extensor muscles, ranging from 1 to 4 according to the modified Ashworth scale (MAS); 3) pain during ankle mobilization rated >4 in the visual analogue scale for pain (VAS), ranging from 0 (no pain) to 10 (unbearable pain); 4) no clinical relapse and no use of corticosteroid and botulinum toxin in the last 6 months. The study was approved by the local Ethics Committee.

A total of 120 subjects (68 women) were examined for study eligibility. At the end of the evaluation, 68 subjects (40 women; mean age±SD: 51.4±12.2 years) met the inclusion criteria and joined the study.

Clinical outcome measures

The primary outcome was pain referred to the treated lower limb, which was measured using VAS for pain. Responders were those subjects who experienced a pain reduction after treatment greater than 33% versus T0.

The secondary outcome was muscle tone of ankle extensor muscles, measured in the supine position by means of the MAS (patient's ankle was moved from a position of maximal extension to maximal dorsi-flexion over a duration of about one second). To accommodate the "1+" modification for numeric analysis, grade 1 was recorded as 1 and 1+ as 1.5.

Further outcome measures were ankle muscle strength and walking speed. Ankle strength in extension was rated according to the Medical Research Council (MRC) for muscle strength. Walking speed was assessed by 10-meter walking test (10-MWT).

The same physician who was blinded to the protocol performed all clinical assessments.

Electrophysiological study

This assessment was performed to investigate the possible effects of RSWT on the stretch reflex excitability. Subjects were tested while lying in a bed relaxed in a prone position with their feet over the edge of an examining table. Special care was taken to assure that muscles acting on the ankle joint were at complete rest. The posterior tibial nerve was stimulated by a surface bipolar electrode placed in the popliteal fossa. Rectangular pulses of 2ms duration were administered by means of a constant-current stimulator (model DS7A; Digitimer, UK). EMG was recorded through bipolar surface preamplified electrodes (TSD150B; Biopac Systems Inc, USA) positioned over the soleus muscle, 3cm below the insertion of the gastrocnemii. M-wave and H-reflex peak-to-peak amplitudes were evaluated by means of the Acqknowledge software (Biopac Systems Inc, USA). At the beginning, for each subject, the soleus H–M recruitment curve was built up using a stimulation frequency of 0.1Hz. The electrical stimulation intensities producing H-max (the H-reflex with the maximal amplitude) and M-max (the M-wave elicited by a supramaximal stimulus) was defined and the H-max/M-max ratio was calculated. Stimulus strength was set (in the ascending limb of the H-reflex intensity curve) to produce H-reflexes having amplitude near to H-max/2 using a frequency of 0.1Hz. Using this stimulation intensity, 20 H-reflexes were collected at 0.1Hz and then 20 H-reflexes were recorded at a frequency of 1Hz. To calculate postactivation depression (PD), the ratio of the H-reflex amplitude evoked at 1Hz to the H-reflex amplitude evoked at 0.1Hz (1Hz/0.1Hz ratio) was calculated in each single subject: the greater the 1Hz/0.1Hz ratio, the smaller the PD.

Radial shock wave therapy (RSWT)

We used a BTL-6000 SWT Topline Unit (BTL Italy). Patients were treated only on one side. When

both sides met the inclusion criteria (hypertonia of ankle extensor muscles ranging from 1 to 4 according to the MAS and pain during ankle mobilization), the treatment was delivered to the most painful side. RSWT consisted of a course of 4 sessions with a 1-week interval between sessions. During each session, 2000 shots were delivered to ankle extensors muscles including the Achilles tendon (600 shots in each gastrocnemius muscle; 600 shots in the soleus muscle; 200 shots in the Achilles tendon). The frequency used was 4 Hz, with a pressure of 1.5 Bars. The treatment was not painful.

Placebo treatment

The placebo treatment was similar to RSWT. However, in the placebo sessions shock waves were prevented from reaching the target muscles by a thin foam cushion placed on the metal applicator.

The therapists delivering RSWT were not blinded. On the contrary, the medical doctors performing clinical and H-reflex measurements were blinded.

Study procedure

Patients were randomly allocated to receive either the RSWT or the placebo treatment after stratification using a software-generated randomization tool. No physiotherapy treatment was performed after the treatment.

The clinical examination was performed: just before the first treatment session (T0); one week after the first session (just before the second session) (T1); one week (T2) and 4 weeks (T3) after the last session.

The H-reflex investigation, performed only in the subjects treated with RSWT, was performed 2 weeks before T0 (baseline) and at T2. The results obtained in patients at baseline were compared with those obtained in healthy subjects.

Statistical analysis

At T0, differences between RSWT and placebo groups were analysed using unpaired t-test (age values) and Mann-Whitney U test (EDSS, MAS, VAS, 10-MWT and MRC scores).

Changes between T0 and post-treatment (T1-T2-T3) clinical measures (MAS, VAS, 10-MWT and MRC scores) were analysed using the Wilcoxon test.

H-reflex parameters (H-max/M-max ratios and 1Hz/0.1Hz ratios) obtained in patients at baseline were compared to those obtained at T2 using paired t-test. H-reflex parameters obtained in patients at baseline were compared to those obtained in healthy subjects using unpaired t-test.

The level of statistical significance was set as $p < 0.05$.

All data are shown as mean ± standard deviation (SD).

Results

Thirthy-four subjects received RSWT and 34 subjects received placebo treatment.

During the period of the study (from enrolment to 4 weeks after the last treatment's session), therapies potentially acting on muscle tone and pain were not modified. In the RSWT group, 25 subjects were treated with baclofen, 10 with benzodiazepines, 12 patients with pregabalin and 2 with gabapentin. In the placebo group, 23 patients were treated with baclofen, 13 patients were treated with benzodiazepines, 10 patients with pregabalin and 2 with fampridine.

Table 1 and table 2 show the pre-treatment (T0) demographic and clinical characteristic of the 68 subjects enrolled in the study. At T0, statistical analysis did not find any significant differences in age distribution, EDSS and clinical outcome measures (VAS for pain, MAS, MRC for muscle strength and 10-MWT) between the subjects treated with RSWT and those treated with placebo.

Table 2 shows the time course of the clinical outcome measures. After RSWT, VAS scores were significantly decreased at all follow-up evaluations with the maximal effect at T2, when the mean pain score decreased from 6.49 to 3.44. Responders were 26% of the subjects at T1, 68% of the subjects at T2 and 32% of the subjects at T3. MAS scores were significantly decreased only at T2, while significant changes were not observed in MRC scores and in the 10-MWT. After the placebo treatment, no significant changes were found from T0 values. There was only one responder after the placebo treatment (3%).

Table 3 shows the results of the H-reflex investigation performed in the patients treated with RSWT and in 40 age-matched healthy subjects (mean age ± SD: 56.44±15.12 years). H-max/M-max ratios and 1Hz/0.1Hz ratios obtained in patients at baseline resulted significantly higher than those obtained in healthy controls. In patients, no significant differences were found between baseline and T2 values.

Discussion

The main finding of this study, performed in MS patients with hypertonia of ankle extensor muscles associated with pain, was that 4 sessions of RSWT induced a significant pain reduction. This effect, peaking 1 week after the last session (T2), was already disclosed 1 week after the first session (T1) and persisted 4 weeks after the last session (T3). At the time of the maximal effect on pain (T2), a reduction of muscle tone was observed. RSWT did not have any significant influence on muscle strength and gait speed (10-MWT). No effect was noted after the placebo treatment.

Both nociceptive and neuropathic pain is a common symptom in MS[17]. In the patients enrolled in the present study, pain was enhanced by ankle mobilization. In the majority, spontaneous pain was increased by passive and active motion of the ankle and a few patients had pain exclusively during ankle mobilization. This dependence from mobilization of the ankle supports the nociceptive nature of the pain, even though a neuropathic component cannot be excluded.

Spasticity can be the direct cause of pain in MS patients[14]. It has been shown in healthy subjects that lengthening a contracted muscle (eccentric contraction) can cause the disruption of some muscle fibers with the release of substances that may excite the muscle nociceptors[18]. The same process is likely to happen when a spastic muscle is stretched. However, it must be stressed that spasticity is only one of the positive signs displayed by patients with UMN syndrome; others include muscle spasms, cocontractions and spastic dystonia. The negative signs are weakness and loss of dexterity[1]. All these positive and negative features along with soft tissue changes perturb body weight distribution, inducing excessive stress on joint structures and causing pain[19]. Sensory disturbances can also play a role. It is the mixing and matching of such components that leads to the pain perceived by the patients with UMN syndrome.

In this complex scenario, the reduction of muscle tone after RSWT is likely to have played only a partial role in the pain relief experienced by the patients investigated in this study. This view is

corroborated when the time courses of the two phenomena are compared. The reduction of pain was present 1 week after the first session (T1) and 4 weeks after the last session (T3), at a time when no effect on muscle tone was detected.

Therefore we believe that the pain reduction that we observed was largely determined by shock wave action on nociception. Although pain relief is the main result reported following RSWT, the antinociceptive mechanisms of shock waves are far from being completely understood. Important mechanisms are thought to be nitric oxid production[20], cytokines inhibition[21] and the modulation of peptides involved in nociception[22].

While the observed results on pain were in line with the literature, our findings on muscle tone lasted for a shorter time that previously reported. One week after the first session of RSWT, we did not find any effect (T1); muscle tone was reduced one week after the last session (T2), but the effect was not maintained one month after the last session (T3).

Indeed previous works, in which RSWT was used to treat hypertonia, showed more enduring results, lasting at least two weeks after the last session[11-13]. We suggest that the discrepancy between our results and the previous ones is probably related to patients' age, disease duration and the level where the UMN are damaged.

Concerning the possible mechanisms of the observed muscle tone reduction, pain relief is one candidate. It is well known that pain itself may be contributing to increased muscle tone[15]. Therefore, treating the pain may reduce muscle tone. In the present study, the reduction of muscle tone was detected only when the effect on pain reached its peak (T2), suggesting that pain reduction must exceed a threshold to determine its effects on muscle tone.

Another mechanism could be the effect of RSWT on muscle fibrosis and other non-reflex components of muscle hypertonia[11]. This mechanism has been originally suggested to explain the reduction of muscle tone induced by ESWT[4,23]. Through its action on non-reflex hypertonia,

however, RSWT could also reduce spasticity. The reduced extensibility, due to soft tissue changes, causes pulling forces to be transmitted more readily to the muscle spindles. In this condition, an exaggerated spindle discharge in response to muscle stretch might lead to an increased stretch reflex[2]. Thus, the reduction of non-reflex hypertonia could modify muscle spindles excitability, leading to a secondary reduction of spasticity.

A third mechanism by which RSWT might act on muscle tone could be the modification of the excitability of the spinal circuits mediating the stretch reflex. Indeed, mechanical stimuli acting on muscles and tendons can decrease spinal excitability[24] and induce long-lasting effects on spasticity[25]. To test this possibility, the excitability of the stretch reflex loop was measured using the soleus H-reflex in all the patients treated with RSWT and in a group of 40 age-matched controls. Specifically, we investigated the H-max/M-max ratio, which is considered an index of spasticity[26]. Furthermore, we evaluated postactivation depression (PD), i.e. the inhibition of the H-reflex induced by a preceding conditioning stimulus able to activate the afferents mediating the H-reflex itself[27]. PD was investigated assessing the frequency-related depression of the soleus H-reflex[26]. We decided to investigate PD because it is highly correlated to the severity of spasticity and it has been used in the longitudinal assessment of spasticity[26,28].

As largely expected, at baseline soleus H-max/M-max ratio was higher and PD was lower in patients than in healthy controls. In the treated MS patients, these parameters remained stable 1 week after the last session of RSWT (T2), when muscle tone was decreased. Our data, therefore, did not support the action of RSWT on the excitability of spinal circuits underlying the stretch reflex and confirmed previous results in stroke patients after ESWT[4,29]. Indeed it is well known that MAS is not able to discriminate reflex and non-reflex hypertonia[30]. The lack of RSWT effects on spinal excitability supports the idea that RSWT is likely to act on non-reflex hypertonia, for example on muscle fibrosis. Further studies are needed to investigate this issue.

After RSWT no adverse effects were observed in any patient. In particular, RSWT did not induce weakness in the treated hypertonic muscles, confirming previous results obtained with both ESWT[4,5,23,29,31-33] and RSWT[11-13].

During the study, patients have not been treated with physiotherapy. This was done in order to refer any changes in outcome measures to RSWT itself. In this connection, the absence of functional changes on gait (speed velocity) did not represent an unexpected result. On the contrary, it confirmed that, to achieve functional results, any physical treatment should be integrated as part of a comprehensive rehabilitation program, in which the role of physiotherapy is essential.

The present is the first study in which shock waves have been used to treat muscle hypertonia and pain in MS patients. This is also the first randomised placebo controlled study in which radial shock waves have been used to treat hypertonia in adult patients. With the limitations related to the lack of an objective assessement of hypertonia and the limited number of subjects, the present study suggests that RSWT can reduce pain and muscle tone in MS patients, without any effect on muscle strength. Further studies are needed to confirm the present results and evaluate their impact on quality of life. To optimise the effect in MS patients and obtain functional results, we think that RSWT should be integrated in a rehabilitation program, where physiotherapy should consist of active and passive stretching of the hypertonic muscles, strength training of the antagonist muscles, functional mobility training and gait pattern training.

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Conflict of Interest Statement

The Authors declare that there is no conflict of interest in relation to this paper.

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Table 1. Demographic and clinical features of subjects before treatment (T0)

	Subjects treated with RSWT	Subjects treated with placebo
Age, years, mean±SD	51.74±11.29	51.00±13.17
Gender, M/F, n	14/20	16/18
Treated side, R/L, n	16/18	16/18
EDSS, mean±SD	6.60±0.78	6.15±1.23

RSWT: radial shock wave therapy; SD: standard deviation; M: male; F: female; n: number; R: right; L: left; EDSS: Expanded Disability Status Scale.

Table 2. Outcome measures (VAS, MAS, 10-MWT and MRC) at the different time points

	VAS (mean±SD)	Responders	MAS mean±SD	MRC for muscle strength mean±SD	10-MWT mean±SD
Subjects treated with RSWT					
T0	6.49±1.60		2.68±0.77	1.88±1.14	34.17±12.68
T1	**5.22±1.53 (p<0.0001)**	26%	2.62±0.74 (p=1)	1.94±1.15 (p=1)	33.14±12.79 (p=0.7)
T2	**3.44±2.07 (p<0.0001)**	68%	**1.90±0.98 (p<0.0001)**	1.99±1.14 (p=0.1)	32.25±12.16 (p=0.07)
T3	**5.21±1.80 (p=0.0004)**	32%	2.56±0.92 (p=0.2)	1.87±1.14 (p=1)	33.05±12.74 (p=0.3)
Subjects treated with placebo					
T0	6.15±1.23		2.56±0.99	2.12±0.98	39.11±14.91
T1	5.62±1.26 (p=0.08)	3%	2.50±1.05 (p=0.4)	2.15±0.74 (p=1.0)	39.63±13.67 (p=0.8)
T2	5.68±1.49 (p=0.2)	3%	2.44±1.05 (p=0.2)	2.18±0.67 (p=0.8)	39.81±14.30 (p=0.8)
T3	5.68±1.30 (p=0.2)	3%	2.47±1.08 (p=0.3)	2.18±0.80 (p=0.8)	40.37±14.39 (p=0.7)

RSWT: radial shock wave therapy; SD: standard deviation; VAS: visual analogue scale; MAS: modified Ashworth scale; MRC: medical research council; 10-MWT: ten-meter walking test. Responders were those subjects who experienced a pain reduction after treatment greater than 33% versus T0.

Table 3. H-reflex results in patients treated with RSWT and in 40 age-matched healthy subjects

	H-max/M-max ratio	1Hz/0.1Hz ratio
Patients at baseline	0.57±0.26	0.62±0.22
Patients at T2	0.56±0.24 (p>0.05)	0.59±0.13 (p>0.05)
Healthy subjects	0.30±0.14 (p=0.000002)	0.47±0.18 (p=0.005)

RSWT: radial shock wave therapy; H-max: the H-reflex with the maximal amplitude; M-max: the M-wave elicited by a supramaximal stimulus. P values refer to the comparison with the results obtained in patients at baseline.