Original Article

Analyzing the Effect of Extracorporeal Shockwave Therapy after Botulinum Toxin Injection on Calf Muscle Spasticity Improvement in Patients with Multiple Sclerosis – A Randomized Clinical Trial

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Abstract

Background: Spasticity is a frequent and disabling manifestation of multiple sclerosis (MS), characterized by increased muscle tone and stiffness that limit mobility and daily functioning. Effective management requires a multimodal therapeutic strategy. This randomized clinical trial evaluated the efficacy of adjunct extracorporeal shockwave therapy (ESWT) following botulinum toxin type A (BTX-A) injection in reducing calf muscle spasticity in MS patients.

Materials and Methods: Twenty participants were randomly assigned to receive either BTX-A alone (n = 10) or BTX-A combined with ESWT (n = 10). Clinical outcomes, including range of motion (ROM), Modified Ashworth Scale, and pain assessed by visual analog scale (VAS), were measured at 10 days, 1 month, and 2 months post-treatment.

Results: Dorsiflexion ROM showed no significant between-group difference ($P = 0.807$), whereas plantar-flexion ROM significantly improved in the BTX-A + ESWT group compared with BTX-A alone ($P = 0.047$). MAS scores declined significantly over time in both groups ($P < 0.001$) without intergroup difference. Pain reduction, assessed by VAS, was greater in the ESWT group, showing significant between-group differences ($P = 0.02$). Compared with BTX-A alone, adjunct ESWT produced greater VAS improvement at day 10 (mean difference − 0.90, 95% CI − 1.65 to − 0.15) and 1 month (−1.10, 95% CI − 1.76 to − 0.44).

Conclusions: ESWT as an adjunct to BTX-A enhances pain relief and improves plantar-flexion ROM in MS-related calf spasticity compared with BTX-A alone, supporting its role as a valuable component of multimodal spasticity management.

Keywords: Botulinum toxin, calf muscle, extracorporeal shockwave therapy, multiple sclerosis, spasticity

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Introduction

Spasticity is a velocity-dependent increase in tonic stretch reflexes accompanied by an increase in tendon jerk (clonus) which affects movement and may lead to muscle pain, stiffness, decreased range of motion, and dysfunction. Spasticity is one of the leading causes of disability in patients with central nervous system disorders and is one of the most common problems in patients with multiple sclerosis (MS).[1] More than half of patients with MS have significant muscle spasticity. Patients with more severe spasticity also show more disability-related issues.[2] Spasticity is also one of the leading

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causes of disability in people with neurological disorders – a movement disorder in which muscle tone increases. There are many treatment strategies for spasticity, including treating the underlying problem, physiotherapy, medication, and focal therapies such as botulinum toxin. In more severe cases, surgical treatments are used.[3,4] Painful muscle spasticity is a common issue in patients with MS. In these patients, muscle tone increases, and pain limits their movement and reduces their quality of life by affecting their daily activities and how they sleep. Drug treatments used to improve spasticity in MS patients include Baclofen, Dantrolene, Benzodiazepines, and Clonidine.[5] Studies show that drug therapies have not been very effective in improving spasticity in patients with MS; therefore, other treatment modalities must be considered to ameliorate the disorder.[6]

Previous studies have used Botulinum Toxin Type A (BTX-A) for treating neurological diseases.[7] In addition, various studies have shown that BTX-A injection is entirely safe and has few side effects while it can significantly reduce spasticity in patients.[8] In spasticity, Toxin's effectiveness begins several days after BTX-A injection and lasts 90 days, with the best effect seen in the first month of injection.[9] Some studies show the beneficial effects of BTX-A injection in patients with MS. A review of the studies conducted on the effect of BTX-A in MS patients indicates that this method can be widely applied in the treatment of muscle spasticity as bladder dysfunction in MS patients.[10] Moreover, a study in 74 MS patients with hip adductor muscle spasticity showed that BTX-A injection could reduce muscle spasticity; also, it was more effective than a placebo.[11]

Several studies have shown the effectiveness of BTX-A in combination with physical therapy; however, the data related to this achievement are still limited. As an instance, a study on MS patients examined physiotherapy's effect immediately after BTX-A injection. Patients were divided into two groups for treatment with BTX-A in combination with traditional physiotherapy (including stretching and range-of-motion exercises) and BTX-A injection alone. This study showed that using physiotherapy with BTX-A is a more effective treatment method to ameliorate muscle spasticity in MS patients.[12]

Other physical therapies without BTX-A, such as Extracorporeal Shock Wave Therapy (ESWT), have been studied to treat spasticity and movement-related disorders.[13] The more application of ESWT to treat spasticity has been reported in studies for various reasons that this method has been effective in improving spasticity.[14] A few years after the first study, the effects of the ESWT method in the treatment of muscular hypertension and movement disorders were evaluated, and spasticity was seen in the flexors of the fingers and wrists. There was no sign of nerve damage, and its therapeutic effects remained for 12 weeks.[15] Another study of 28 patients with stroke-induced plantar flexor spasticity compared the effect of ESWT with a control group and reported that ESWT improved spasticity and reduced pain.[1]

Although BTX injection is the standard of care for treating spasticity, incomplete response and short-time efficacy can be enhanced with adjunct modalities. The current study evaluated applying the ESWT method in combination with BTX-A injection, which was assessed in a different group of patients.[13] No study has evaluated this modality's efficacy with BTX-A on MS patients. Thus, due to the high incidence of spasticity in MS patients, we decided to evaluate and compare the therapeutic effectiveness of ESWT after the injection of BTX-A in reducing calf muscle spasticity in MS patients based in Isfahan.

Materials and Methods

Study population

This study was designed as a randomized clinical trial (RCT) in patients with multiple sclerosis and calf muscle spasticity who were referred to tertiary clinics at AL Zahra and Kashani hospitals of Isfahan University of Medical Sciences from March to September 2020. This research has been conducted following the Declaration of Helsinki.

Randomization and allocation concealment

Participants were randomized 1:1 to receive either BTX-A alone (Group A) or BTX-A plus ESWT (Group B) using a computer-generated simple random sequence prepared by an investigator not involved in enrolment, treatment, or outcome assessment. Allocation codes were placed in sequentially numbered, opaque, sealed envelopes that were opened by the clinic nurse only after baseline assessments were completed. Outcome assessor(s) and the statistician remained blinded to group allocation throughout data cleaning and analysis.

Sample size and grouping

The sample size was calculated based on the statistical formula for comparing means in RCTs with the standard deviation for Modified Ashworth's Scale (MAS) obtained from a previous study[16] (10 participants for each group). The participants were enrolled using a consecutive sampling method. Random assignment was done via random allocation online software. We randomly divide these numbers into two parts. Each group code was written on paper and placed in an envelope. The patient then was assigned to one of the two groups. One researcher selected the study sample (SH). Inclusion criteria were a definitive diagnosis of multiple sclerosis (MS) by a neurologist based on the revised McDonald Criteria[17], presence of calf muscle spasticity (Modified Ashworth Scale score >1+), age between 18 and 55 years, ability to provide informed consent, and willingness to participate in follow-up assessments. Exclusion criteria included the presence of cognitive impairment that interferes with cooperation, peripheral nerve disease or myopathy, pregnancy, use of a pacemaker, history of Botulinum toxin injection within the previous 6 months, significant calf muscle atrophy, coagulation disorders, and history of surgery or fractures at the spasticity.

Data collection

At first, the patient was interviewed, and demographic

information, including name, age, sex, and education, was extracted and recorded in a particular form specified for each patient. In the second phase, information related to the disease, including the duration of MS, the duration of spasticity, and the severity of MS, was asked for and entered in a particular form for the patient. Then the passive range of motion scales, MAS, and VAS were calculated for each patient and recorded in the form.

The physical medicine clinic divided patients into two equal groups using a random allocation system. In the first group (A), only Botulinum Toxin injection with BTX-A was performed for the patient under the standard protocol. For this purpose, 100–200 mU of BTX-A, Dysport was used, which was injected in the medial and lateral head of the calf muscle based on the intensity of their spasticity. The second group (B) was treated with ESWT after injection. A Shockwave device was used for ESWT treatment. For this purpose, the radial head was used, and the corresponding frequency was 8 Hz. The number of shocks was 2000 on the gastrocnemius muscles, 600 on the soleus muscle, and 200 on the Achilles tendon. The number of sessions was five sessions once a week. A Shockwave device (Storz Medical-Duolith SD1) was used for ESWT treatment. The radial head was applied at a frequency of 8 Hz, with 2000 shocks on the gastrocnemius muscles, 600 on the soleus muscle, and 200 on the Achilles tendon, in five weekly sessions, following previously published protocols.[18,19] Immediately after treatment, 10 days, 4 weeks, and 8 weeks after the intervention, patients were reinvited. MAS, passive range of motion, and VAS scales were completed for patients and entered in a particular form for each patient. Also, in case of any complication in the patient, it was treated by the relevant physician, and the patient was excluded from the study. The outcome assessor and statistician were kept blind in this single-blind clinical trial.

Data collection tools

1. Modified Ashworth's Scale (MAS) is a scale for examining muscle spasticity that varies from 0 to 4. The number zero indicates normal muscle, and the number 4 indicates rigid flexion.[20] This questionnaire was translated into Farsi. Nakhostin Ansari *et al*.[20] examined its validity and reliability in 2012, which was between 0.81 and 0.91. The Farsi version of this questionnaire has been used in other similar studies, and its results have been compared.
2. Passive Range of Motion: With the goniometer, the motion range of the patient's knee and ankle joints is measured. This device has been widely applied in various studies related to spasticity. Also, its validity and reliability have been confirmed.[19]
3. The Visual Analogue Scale (VAS) is a small scale for pain intensity ranging from 0 to 10. The number zero means painlessness, and the number 10 means the most severe pain a person has ever experienced.[21] This scale has been widely used in pain-related research, and its validity and reliability have been confirmed.

Clinical implications

Adding rESWT after BTX-A is feasible, is noninvasive, and—based on the present data—can accelerate pain relief within the first month and may aid plantar-flexion ROM. Clinicians may consider integrating rESWT into post-BTX rehabilitation for MS-related calf spasticity while continuing to monitor tone (MAS) and function; patient selection and dose-parameter optimization should be individualized.

Interpretation of nonsignificant findings

Lack of between group differences in dorsiflexion ROM and MAS may reflect (i) limited statistical power (n = 10 per arm), (ii) baseline imbalances in ROM that favor larger within-group gains without achieving between-group separation, (iii) measurement variability inherent to goniometry, and (iv) the mechanistic profile of rESWT—targeting musculotendinous stiffness and nociceptive modulation—which may translate more readily into plantar-flexion ROM and pain than into velocity-dependent tone (MAS). Future trials with larger samples and baseline-adjusted mixed models are warranted to clarify these effects.

Safety profile

The absence of serious adverse events and only transient local soreness are consistent with the known safety of both BTX-A and rESWT when applied with standard parameters in neurorehabilitation settings.

Data analysis

Demographic characteristics were described with frequency, percentage, mean, and standard deviation. First, the normality of the data distribution was checked for analytical purposes. In the case of normal distribution, an independent *t*-test was used to compare the differences between the groups. In the absence of a normal distribution, their nonparametric equivalents, the Mann–Whitney test, were applied. The Repeated Measures test performed comparisons between groups at different times. A P value <0.05 was considered the statistical significance level, and all statistical analyses were performed in SPSS version 21 software.

Results

This study includes 20 patients, 12 females 27–48 y/o and eight males 30–45 y/o. Patients were randomly assigned to the Botulinum Toxin Injection group (group A), which received BTX-A injection; ten other people were assigned to another group (B) that received Botulinum Toxin Injection in combination with ESWT. In each group, there were three males (30%) and seven females (70%). The mean and standard deviation of age in groups A and B were 39.90 ± 6.78 and 40.80 ± 6.87 years, respectively. The average duration of the disease in groups A and B was, respectively, 9.70 ± 2.62 and 9.90 ± 2.23 years. In this study, the severity of MS disease was reported in Table 1, which was not significantly different between the groups (P = 0.389).

In this study, the amount of inactive ROM was evaluated as dorsiflexion and plantar flexion in four-time intervals: before and 10 days, 1 month, and 2 months after the intervention. Also, the two groups were compared with each other. Table 2 and Figure 1 show that dorsiflexion ROM did not differ significantly between the two groups ($P = 0.807$) at the mentioned time points; however, three were significantly larger plantar flexion ROM in group B compared to group A at 10 days, 1 month, and 2 months after the intervention ($P = 0.047$).

In this study, the amount of MAS in four-time intervals, before the intervention and 10 days, 1 month, and 2 months after the intervention, was evaluated, and the two groups were compared; the results are shown in Table 2 and Figure 1. Based on the results, the amount of MAS showed no significant difference between the two groups, but in each group with increasing follow-up time, the amount of MAS had a significant decreasing trend ($P < 0.001$).

Furthermore, this study evaluated the amount of VAS in four intervals: before the intervention and 10 days, 1 month, and 2 months after the intervention. The two groups were compared, as shown in Table 2. Based on the results, the amount of VAS showed a significant difference between the two groups, so in the group treated with ESWT with increasing time, the amount of VAS significantly decreased ($P = 0.02$).

Table 1: Frequency distribution of multiple sclerosis disease severity

Variables	Frequency (%)		*P*
	Control	ESWT	
Cane	2 (20)	3 (30)	0.389
Wheelchair	1 (10)	1 (10)	
Walker	0 (0)	2 (20)	
No	7 (70)	4 (40)	

Between-group effect sizes and confidence intervals

Between-group differences favored BTX-A + ESWT for pain reduction at day 10 (mean difference −0.90, 95% CI −1.65 to −0.15; large effect) and 1 month (−1.10, 95% CI −1.76 to −0.44; very large effect). Differences in plantar-flexion ROM favored the ESWT group (moderate effects), although confidence intervals included the null [Table 3].

Adverse events

No serious adverse events occurred in either group during the 8-week follow-up. A small number of participants reported transient post-session soreness at the treatment site; all cases resolved spontaneously without intervention.

Discussion

The present study attempts to evaluate the effect of ESWT after Botulinum Toxin Injection on calf muscle spasticity improvement in patients with multiple sclerosis. Based on the results, the amount of dorsiflexion ROM did not differ significantly between the two groups that participated in the study; however, the amount of plantar flexion ROM showed a significant difference between the two groups ($P = 0.047$). The amount of VAS also showed a significant difference so that, over time, the amount of VAS in the group treated with ESWT had a significant decreasing trend ($P = 0.02$).

Among therapeutic approaches, Botulinum Toxin administration is extensively used for post-stroke spasticity, which has recently been widely confirmed for its effectiveness in improving MS.[22] This treatment has been safe and effective for up to 90 days.[9] However, it is aggressive and painful at the injection site.[23] For better accuracy and to prevent erroneous propagation in adjacent tissues, echo guidance is required.[24] In addition, existing commercial preparations of Botulinum Toxin contain human and nonhuman proteins that may act as antigens and elicit immune responses. Also, they are generally

Table 2: Comparison of indices range of motion modified Ashworth's scale and visual analog scale in multiple sclerosis patients

Variables	Control Group					ESWT Group				
	Before	After 10 Days	After 1 Month	After 2 Months	*P*	Before	After 10 Days	After 1 Month	After 2 Months	*P*
D-ROM	15.30±2.05	26.50±2.41	27.00±2.58	25.50±2.83	<0.001	9.70±3.46	27.10±7.72	29.20±4.89	29.70±7.13	<0.001
P-ROM	10.11±2.02	13.88±4.85	14.44±4.63	12.66±2.54	<0.001	16.20±5.34	16.70±6.05	17.70±7.79	15.90±6.10	<0.001
MAS	3.20±0.42	1.70±0.67	1.10±0.56	0.90±0.31	<0.001	3.40±0.51	1.40±0.69	0.70±0.67	0.40±0.51	<0.001
VAS	5.30±0.48	2.70±0.94	2.00±0.47	1.00±0.00	<0.001	5.40±0.84	1.80±0.63	0.90±0.87	0.40±0.51	<0.001

All data were shown into mean±SD. D-ROM: Dorsiflexion ROM, P-ROM: Plantar flexion ROM, *P*: Repeated Measure Test for each group

Table 3: Effect size was shown in this table

Outcome and Time	Mean diff (B−A)	95% CI	Cohen's *d*	Interpretation
VAS, day 10	−0.90	−1.65 to −0.15	−1.12	Large, favors ESWT
VAS, 1 month	−1.10	−1.76 to −0.44	−1.57	Very large, favors ESWT
P-ROM, 2 months	+3.24°	−1.15 to +7.63	+0.69	Moderate; CI overlaps 0
P-ROM, 1 month	+3.26°	−2.76 to +9.28	+0.51	Moderate; CI overlaps 0

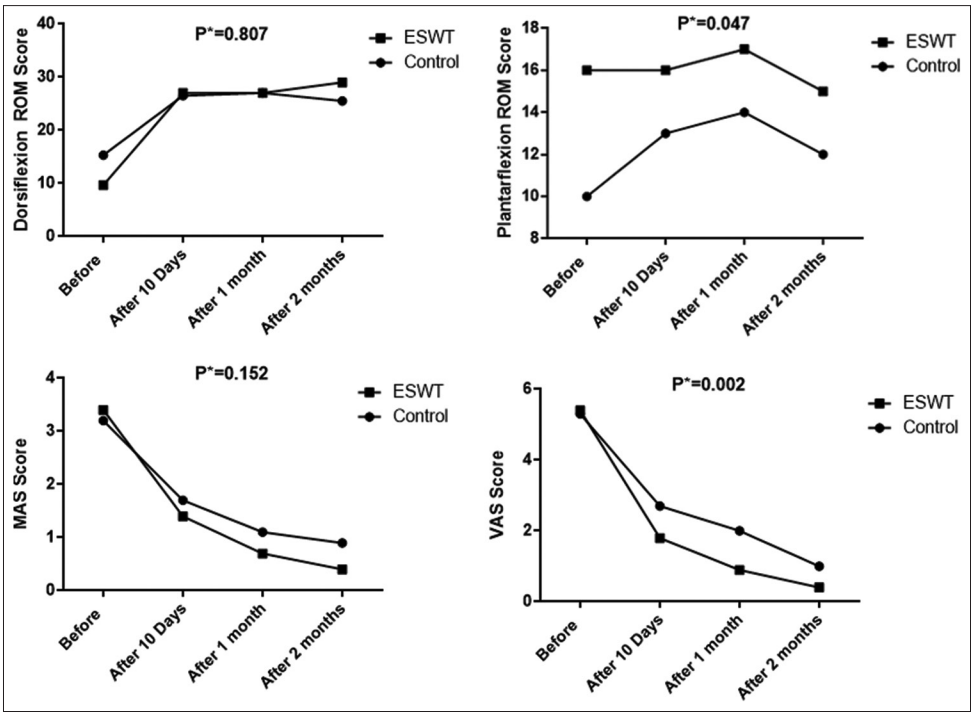

Figure 1: Temporal trajectories of dorsiflexion ROM, plantar-flexion ROM, MAS, and VAS across baseline, day 10, 1 month, and 2 months in the BTX-A (control) and BTX-A + ESWT groups. Lines denote group means; error bars depict SD. ESWT shows earlier and larger reductions in VAS, while changes in MAS occur over time in both groups without a between-group separation; plantar-flexion ROM tends to favor ESWT at follow-ups

dose-dependent and positively correlated with cumulative doses.[25] Shorter injection intervals (i.e. 2 months apart) may increase the risk of neutralizing antibody formation and lack of therapeutic response, indicating longer injection intervals in the standard clinical procedure.[26] For the reasons mentioned above, Botulinum Toxin is limited in providing the maximum injection dose, which requires a long interval between two injections (more than 4 months).

Long-term continuation of Botulinum Toxin treatment in MS patients is limited by the loss of effect, side effects, and lack of regular rehabilitation.[27] Various adjuvant therapies have been proposed to be combined with Botulinum Toxin to enhance its neuroprotective effect. To combine physical therapy for treating limb spasticity in stroke with Botulinum Toxin, ESWT was considered better for some postinjection outcomes, including MAS, spasticity frequency, and pain compared with electrical stimulation. ESWT is a simple, noninvasive treatment and can be repeated over time, without immunosuppressive doses, with effectiveness in the focal treatment of spasticity in stroke, primary CP, and MS.[16]

In this study, patients were divided into two groups. In the first group, only Botulinum Toxin injection with BTX-A was performed under the standard protocol for the patient. For this purpose, 100–200 mU of Botox Type A Dysport was used in the medial and lateral heads of the calf muscle based on the severity of their spasticity. The second group was treated with ESWT after injection. For this purpose, the energy radial head bar4 was used. The number of shocks was 2000 on the gastrocnemius muscles, 600 on the soleus muscle, and 200 on the Achilles tendon. The number of sessions was five sessions once a week. The short duration of the effect of ESWT, although at odds with stroke and CP studies, is entirely consistent with MS data[28] and can be explained by the inherent pathological characteristics associated with the ESWT mechanism of action. In addition, the more limited effect of ESWT over time cannot be attributed to the small number of treatment sessions because, given that the effect of spasticity seems to grow exponentially with the number of sessions, it has a maximum effect in four sessions.[29]

Based on the results, the amount of dorsiflexion ROM did not differ significantly between the two groups. However, the amount of plantar flexion ROM showed a significant difference between the two groups. Due to its performance characteristics, the inactive ROM highlights the presence of contraction and stiffness. The consensus on movement disorder in the IAB-interdisciplinary working group indicates that Botulinum Toxin does not affect the mechanical changes of hypertension. On the other hand, ESWT is involved in inactive ROM by destroying the functional bond between actin and myosin, reducing the inherent stiffness of connective tissue, and increasing muscle development.[16] Hence, our results could be rooted in the overlap between the effect on the neural component obtained by Botulinum Toxin and the effect on the biomechanical component induced by ESWT. Hence, the synergistic application of two types of treatment is of high importance.

Both interventions used in this study are generally considered safe. The most commonly reported side effects in previous

studies include transient local pain, mild swelling, or temporary soreness at the treatment site. In our study, a few patients experienced mild discomfort or tenderness after ESWT sessions, which resolved spontaneously within 24 hours without medical intervention. No serious adverse events were observed during the study period.

Conclusions

Based on the results of the present study, the application of ESWT after Botulinum Toxin injection effectively improves calf muscle spasticity in patients with multiple sclerosis in VAS and plantar flexion ROM index compared to Botulinum Toxin injection. Also, we suggest further studies with larger and more diverse sample sizes on different groups of muscles for more robust conclusions in MS patients.

Authors' contribution

SH, MG, BV, and VS contributed to the conception of the work. SH and MG contributed to the study design, data search, data acquisition, data analysis, interpretation of data, and manuscript preparation. BV and VS contributed to the interpretation of data and manuscript revision. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This trial was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC1398.351). The protocol was registered in the Iranian Registry of Clinical Trials (IRCT20200825048515N41) on 27/09/2021. Enrolment began in March 2020; registration therefore occurred retrospectively, and the reasons for the delay are acknowledged.

Consent for publication

All methods and experimental protocols were approved by the Ethics Committee of the Isfahan University of Medical Sciences. Written consent was obtained from the patients.

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Conflicts of interest

There are no conflicts of interest.

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