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Focal shock waves increase efficacy and prolong the effect of botulinum toxin on spasticity in patients with brain injury from stroke and multiple sclerosis

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Marrero assisted in the revision of the manuscript. All authors have contributed equally to the manuscript and have read and approved the final version of the manuscript.

Data availability- the data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

The preliminary results of this paper were presented as oral communications at the IX SETOC congress, the IV ONLAST congress and the VI ISMST Basic Research Meeting celebrated on 25-26 of March 2022 in Madrid. It received the award for best oral communication.

ABSTRACT

Objective: Assess the effects on spasticity reduction of the association between focal extracorporeal shock wave therapy and botulinum toxin type A, versus the toxin only in brain injury patients.

Design: Eighteen patients were included. The study had two phases: the first phase was observational, and botulinum toxin type A was used. The second was a prospective, deliberate intervention phase in which the toxin was injected and focal extracorporeal shock wave treatment was added (1 sessions/week, for three weeks). The patients were followed up in the 1st, 4th and 6th month, the Ashworth Scale criterion was applied and, for those with lower limb involvement and changes in walking the 10-metre walk test was used.

Results: Patients treated with toxin only showed a statistically significant improvement in spasticity, with 1 point on the Ashworth Scale from week 5, which disappeared at week 17. However, the combined therapy reduced spasticity by 2 points from week 1 to week 25 ($p< 0.001$), with a faster result in the 10-meter gait test ($p= 0.004$).

Conclusion: Combined and simultaneous treatment with botulinum toxin and focal extracorporeal shock wave reduced spasticity in a more effective and prolonged way than treatment with botulinum toxin only.

Key words: Extracorporeal shock wave; Botulinum toxin type A; Spasticity; Stroke; Multiple sclerosis.

What Is Known

-Botulinum toxin type A in patients with stroke and multiple sclerosis reduces spasticity by one point on the Ashworth scale. This effect was maximal at 4 weeks and was maintained for 4 months.

-Focal shock waves reduce spasticity by one point in patients with stroke and multiple sclerosis.

What Is New

-Simultaneous, combined therapy of focal shock waves and botulinum toxin type A in patients with stroke and multiple sclerosis reduces spasticity by two points and improves the gait speed. This effect is maximal from the first week and lasts up to 6 months.

INTRODUCTION

Spasticity is a complication in patients with brain injury, [such as stroke and multiple sclerosis (MS)], and its therapeutic approach is a great challenge due to its effects on the body, requiring complex and multidisciplinary treatment [1-3]. It is defined as: "A motor disorder that is characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex as a component of the upper motor neuron syndrome" [4].

The prevalence of both diseases is varied. In stroke, approximately 20-40% of patients will suffer spasticity at some point in their lives after the event [5], while in MS the percentage increases to 60-90% [6].

This disorder generates a series of changes in the muscle structure, such as chronic pain, joint stiffness, fibrosis, muscle spasms and atrophy [1,7,8]. Spasticity occurring in the upper limbs generally affects the flexor muscles, while in the lower, it tends to affect the extensor muscles [9]. Therefore, this will cause functional limitations that will affect the quality of life, generate disability, and reduce the patient's independence. In addition to this, it can produce great emotional impact and there are great costs involved: [1,6] up to four times compared to the costs of patients with brain injury who do not have spasticity [10]. For these reasons, a therapeutic plan is needed to improve the management of spasticity and optimize the resources.

Over the years, different therapeutic options have been developed to reduce spasticity: pharmacological [e.g., dantrolene, tizanidine, intrathecal baclofen, gabapentin, benzodiazepines,

or botulinum neuro toxin type A (BoNT-A)], surgical (e.g., rhizotomies, tenotomies or tendon grafts), physiotherapy (kinesitherapy, thermotherapy, cryotherapy, and electrostimulation), nerve blocks (radiofrequency and phenol injections), and occupational therapy [1,2,11].

Botulinum toxin type A is an effective and widely used pharmacological treatment to reduce increased muscle tone by selectively inhibiting the release of acetylcholine (ACh) at the neuromuscular junction [12-14]. However, one of the main problems associated with its long-term use is the need for frequent infiltrations, -every 4 months-, and the formation of neutralizing antibodies after repeated doses [12].

In recent years, significant scientific evidence has shown that extracorporeal shock wave therapy (ESWT) on spasticity [3,15,16] is a safe, effective, and non-invasive treatment in MS and stroke [2,17-20].

These two highly effective treatments are often used separately and there is little scientific evidence of their combined treatment [12,14, 21-23].

The main objectives of this study were the following:

1. Assess the effect of the association between focal extracorporeal shock wave therapy (fESWT) and BoNT-A treatment in patients with brain injury Nuevo secondary to stroke or MS on spasticity reduction.
2. Study whether fESWT modifies the duration of the effect of BoNT-A on spasticity.

METHODS

Study design

This study was conducted in two stages: the first phase was observational and used only botulinum toxin. The second was a prospective, deliberate intervention phase in which botulinum toxin was combined with shock waves. The study was performed between January 2020 and May 2022 in outpatients, who gave their informed consent and had all their doubts clarified prior to the start of the study, in accordance with the Declaration of Helsinki. We provided patients with a written informed consent form that, along with the study, was approved by the Drug Research Ethics Committee. The second stage had a 6-month follow-up period. Both phases included 18 adult patients, aged 20-70 years, with brain injury secondary to stroke or MS of subacute and chronic evolution (Table 1), and with spasticity on the Ashworth Scale scores of 2, 3 or 4 in the affected muscles. To compare both treatment schemes, the AS score criterion was used. This study matches all the items of the TIDieR checklist, http://links.lww.com/PHM/C509 -STROBE and reports the required information accordingly (see Supplementary Checklist, http://links.lww.com/PHM/C508).

Interventions

Shockwave therapy was performed using a Duolith® SD1-T Top (Storz Medical) electromagnetic fESWT device, with a EFD of 0.1 mJ/mm^2 and 1500 impulses at a frequency of 5Hz [2,9]. They were applied weekly for three consecutive weeks on the pectoralis major or subscapularis, the upper limb (elbow or wrist or finger flexors) and the lower limbs (rectus femoris quadriceps or triceps surae or tibialis posterior) depending on the spasticity of each

patient (Table 1). Afterwards, they underwent a review and evaluation of spasticity 1 month after the third session of fESWT and 4 and 6 months after the start of treatment (Table 2).

This fESWT regimen was added to the patients' usual BoNT-A treatment, using Dysport® from Ipsen in the lower limb, it was applied at the optimal doses based on the recommendations of each type of toxin [24] and diluted in 1 ml of 0.9% saline, except for abobotulinumtoxinA in the triceps surae, which was diluted in 2 ml. For safety and accuracy, a Logiq V2 ultrasound system (GE Healthcare Systems®, New York, USA) with a linear probe (Freq=8-12 Hz) was used during the administration of BoNT-A. In addition, all patients received rehabilitation during the treatment and follow-up. The rehabilitation treatment in the upper and lower limb consisted of kinesitherapy and relaxation techniques in the spastic musculature, along with occupational therapy in the upper limb and gait re-education in patients with lower limb spasticity.

Measures

Patients were assessed using the Ashworth Scale (AS) and in those with lower limb spasticity, the 10-metre walk test (10MWT) was used. The AS measures muscle resistance during passive stretching with values ranging from 0 to 4, with 0 indicating no increase in muscle tone and 4 indicating that it is impossible to mobilize the affected joint [25]. We evaluated the infiltrated muscles in each patient according to their spasticity pattern. The 10MWT assesses how long it takes the patient to walk 10 m in a straight line, and it is measured in seconds[26]. The change in the use of technical aids (elbow crutch, walker, wheelchair, or electric wheelchair) after treatment and during the follow-up period was also evaluated.

Statistical analysis

For the statistical analysis, each follow-up week the analyzed markers (AS, 10MWT and technical aids) were summarized in medians. These medians were plotted as a function of week, and the changes in the spasticity of the combined treatment were compared with those produced by BoNT-A treatment in patients who had previously been treated with it only. Since the data generally deviate from the normality hypothesis, comparisons between paired data were performed using the Wilcoxon test for paired data, which is independent of the distribution of the data. The hypothesis testing was considered statistically significant when the p-value was less than 0.05. The data were analyzed using the statistical package, version 3.6.1 (R Development Core Team, 2019).

RESULTS

We observed a statistically significant improvement in spasticity that correlated with a decrease in the scores obtained by applying the Ashworth Scale to the affected upper or lower limb musculature and an increase in walking speed in the 10MWT. Despite this at week 7 there was a slight increase in the time of the test in patients with lower limb involvement (Table 3). Although the patients continued to use the same technical aids as before the combined treatment, the improvement in spasticity started from the first week and was maintained until week 25 of follow-up. An improvement in spasticity was observed both in patients who were previously treated with BoNT-A only and in those who received the combined treatment, with 1 point for those treated with BoNT-A from week 5 and 2 points in those treated with BoNT-A and fESWT from the first week (Tables 3 and 4). These results were statistically significant (Table 3 and Figures 1-2). Also, these differences in spasticity reduction between the two treatments were

statistically significant at weeks 5 (Figure 1) and 17 (Figure 2), with $p< 0.001$ and $p=0.0156$, respectively. The reduction in spasticity in patients treated with BoNT-A only disappeared at week 17 (Table 4 and Figure 3), whereas in those treated with BoNT-A and fESWT it was maintained until week 25 (Table 3 and Figure 3). The patients tolerated the shock wave treatment very well, presenting only transient discomfort when applied in the proximity of bony surfaces. No skin reactions were observed during the application or at the end of the treatment.

DISCUSSION

This is the first study of a simultaneous and combined treatment with BoNT-A on spasticity in patients with brain injury secondary to stroke and MS, a follow-up of 6 months period was carried out and we observed an improvement in spasticity of 2 points in AS from the first week of treatment, which was maintained for 25 weeks. This was in comparison to treatment with BoNT-A only, which achieved a 1 point reduction in AS after 5 weeks of treatment and which was maintained for 17 weeks. This effect of BoNT-A only on spasticity is usually achieved with this drug in patients with stroke [27] and MS [21,28]. Regarding the combined treatment of BoNT-A and fESWT on spasticity, few studies have been performed to date [21-23], of which only two have been conducted in patients with brain injury due to stroke or MS [14,23].

The SBOTE study [14] was the first study to combine BoNT-A and fESWT in patients with stroke and compared BoNT-A and electrostimulation administration. The results showed that fESWT was superior to electrostimulation in the improvement of the effect of BoNT-A on spasticity reduction, improving it by 2 points in AS, same as in our study, but in this case, patients were only followed up for 3 months. In a study conducted in patients with MS [21], radial shock waves

(rESWT) were not associated with BoNT-A simultaneously, but 4 months after the BoNT-A treatment instead, and it was followed up only for 3 months. This study observed a spasticity reduction of less than 1 point in AS and prolonged it for 2 months.

In our study, the simultaneous treatment of BoNT-A and fESWT achieved a 2-point reduction on spasticity in AS, an effect that lasted until the sixth month of follow-up. Such reduction was shown to be statistically significant despite the small sample size. This greater effectiveness of the combined and simultaneous treatment of BoNT-A and fESWT indicates the sum of the effects of both methods. In patients treated for spasticity in the lower limb, it was correlated with an improvement in function, and objectified by a progressive reduction in the 10MWT, which resulted in an increase in the walk speed of patients.

BoNT-A has been shown to exert a presynaptic effect by inhibiting the ACh release in presynaptic axons at the neuromuscular junction [29]. However, the exact mechanism by which ESWT reduces spasticity remains a subject of study and discussion [14, 21-23]. In a recent study in Sprague Dawley rats [30] using a session of rESWT on the gastrocnemius muscle of the left paw, with a low-energy EFD (as used in our study), scanning electron microscopy showed destruction of the neuromuscular junctions in the treated area. This induced a transient dysfunction of nerve conduction [30], which would support a postsynaptic effect of shock waves.

In addition, previous studies have shown that ESWT acts on muscle rheology, as the transmitted vibrations break the functional junctions between actin-myosin filaments and reduce connective tissue stiffness [1,12]. Through mechanotransduction ESWT produce biochemical changes that

generate molecular mediators, and that stimulate angiogenesis, improve microcirculation and promote tissue regeneration [2,10,20]. Furthermore, the reduction of spasticity with combined but successive treatment of BoNT-A and fESWT in MS patients [21] was less than that obtained in our study. Based on the above, we suggest that the effect of fESWT when administered simultaneously with BoNT-A could be mediated through a postsynaptic effect, in addition to the presynaptic effect of BoNT-A at the neuromuscular junction.

This study has some limitations, the sample size was small, and the patients were treated and evaluated by the same physician. Nonetheless, our findings demonstrate that a combined treatment would allow a better control of spasticity in patients with stroke and multiple sclerosis by increasing the efficacy of botulinum toxin and prolonging its effect.

CONCLUSIONS

From the results obtained, we can conclude that the simultaneous and combined treatment of fESWT and BoNT-A increases the efficacy of BoNT-A to reduce spasticity and prolongs its effect over time. It also improves the patient´s walking speed and increases the time intervals of BoNT-A injections.

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FIGURE LEGENDS

FIGURE 1. **Representation of spasticity reductions at five weeks in AS** using box-and-bar plots. The lower and upper segments of the rectangle correspond to the 25th and 75th percentiles, respectively. The middle segment corresponds to the median (—). The lower and upper segments correspond to the extremes of the distribution. The circles (o) are outliers.

FIGURE 2. **Representation of spasticity reductions at seventeen weeks in AS** using box-and-bar plots. The lower and upper segments of the rectangle correspond to the 25th and 75th percentiles, respectively. The middle segment corresponds to the median (—). The lower and upper segments correspond to the extremes of the distribution. The circles (o) are outliers.

FIGURE 3. **Comparative effect on spasticity in the Ashworth Scale of patients treated with BoNT-A only, and later-with BoNT-A and fESWT.**

Figure 1

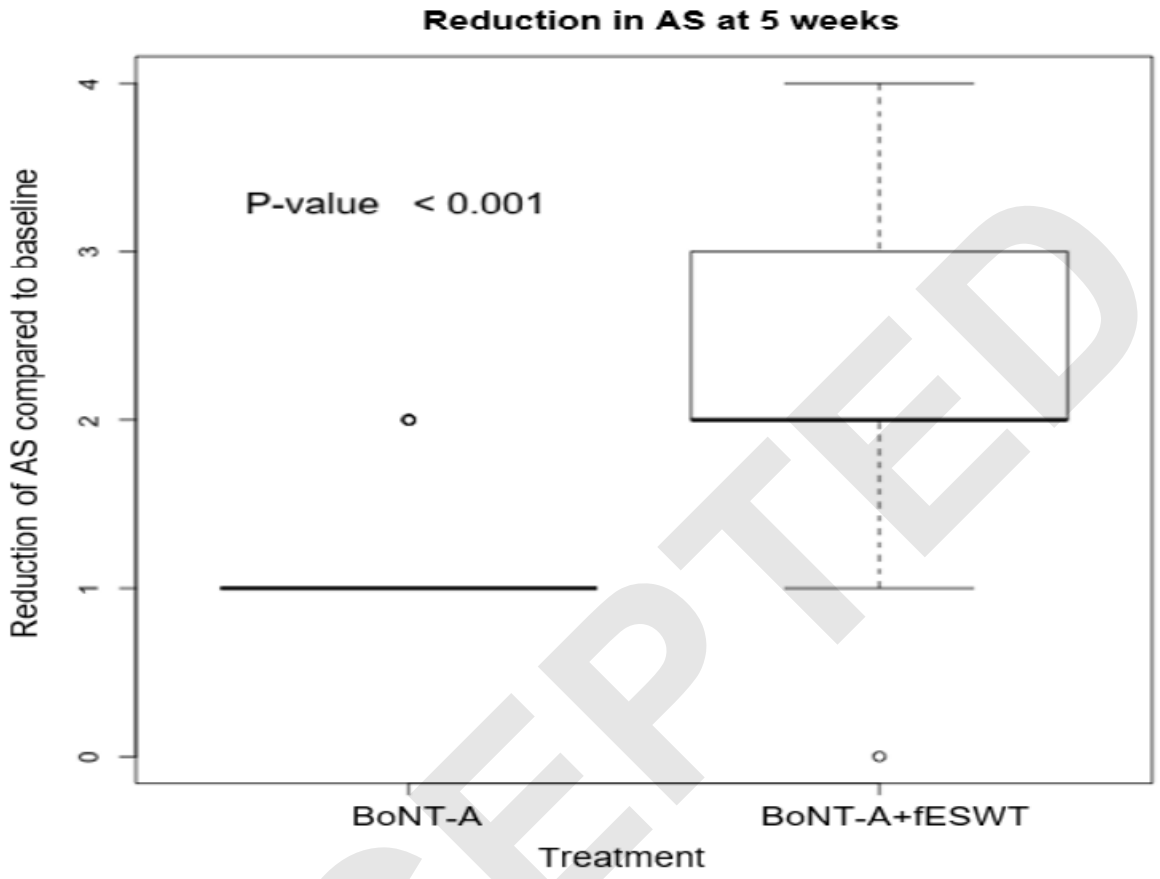

Figure 2

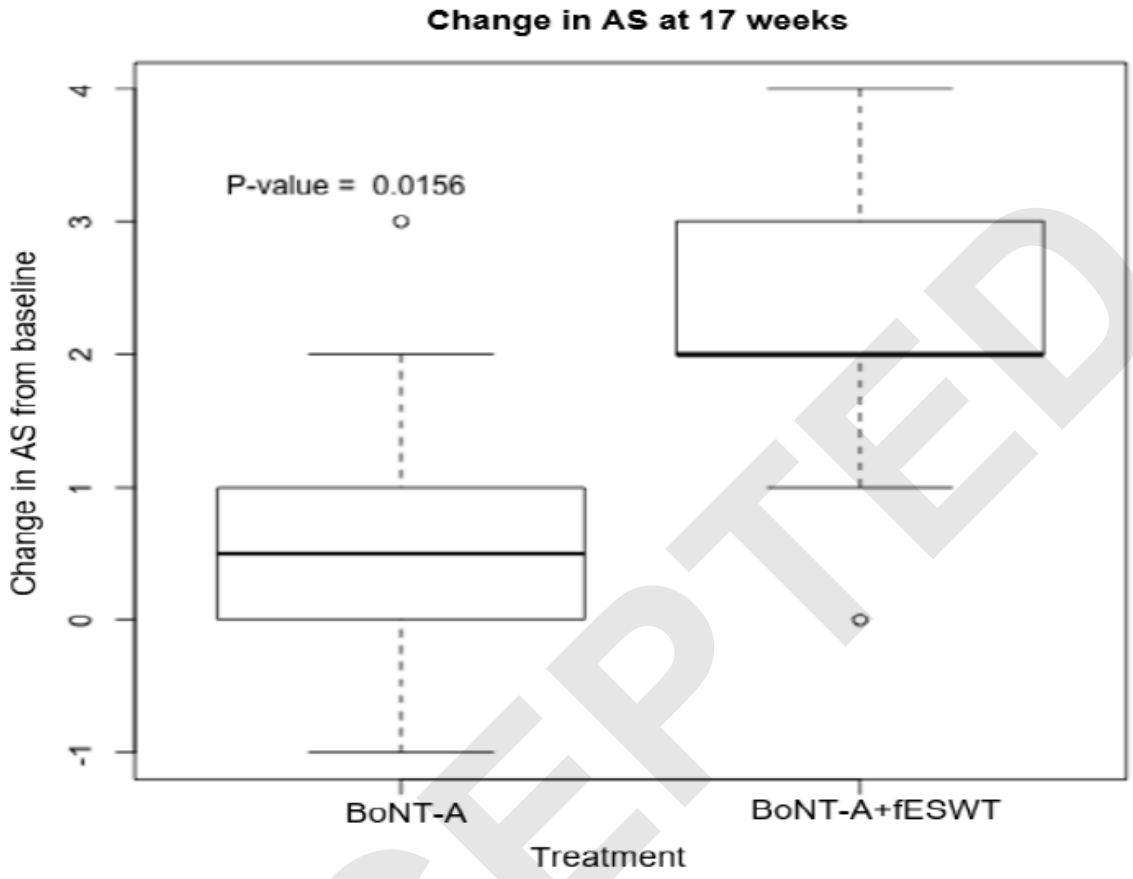

Figure 3

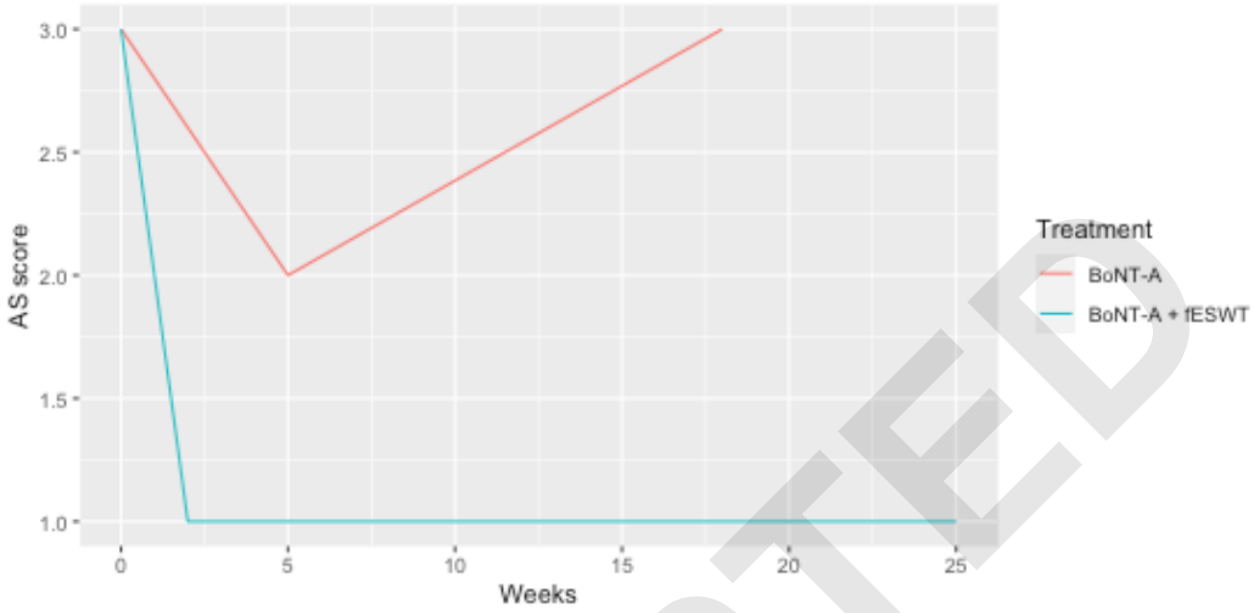

TABLE 1. Patient´s characteristics.

Patient	*Age*	*Sex*	*Diagnostic*	*Evolution*	*Spastic muscles*
1	45	F	MS	Chronic	TS
2	51	F	MS	Chronic	C, TS
3	59	F	MS	Chronic	EF
4	45	M	MS	Chronic	TS
5	51	F	MS	Chronic	TS
6	37	M	MS	Chronic	WF
7	44	M	MS	Chronic	TP, TS
8	55	M	MS	Chronic	PM
9	53	M	Stroke	Chronic	PM, S, TS
10	56	M	Stroke	Chronic	TS
11	20	M	Stroke	Subacute	TS
12	70	F	Stroke	Chronic	C, TS
13	47	M	Stroke	Chronic	C.TS
14	54	F	Stroke	Chronic	PM, S, A
15	61	M	Stroke	Chronic	TP
16	45	F	Stroke	Chronic	TS
17	78	M	Stroke	Chronic	EF, FF
18	72	F	Stroke	Chronic	TS

F:female; **M**:male. **A**:adductors; **C**:rectus femoris cuadriceps;

EF:elbow flexor; **FF**: finger flexor**; PM**: pectoralis major;

S: subscapularis; **TP**:tibialis posterior; **TS**:tricep surae;

WF:wrist flexor

TABLE 2. Combined treatment guideline (BoNT-A+fESWT) and observation period.

Week	***Treatment***	***Observation***
0	BoNT-A+1st fESWT session	Pre-dose
1	2nd fESWT session	1st session effect
2	3rd fESWT session	2nd session effect
7	-	3rd session effect
17	-	3rd session effect
25	-	3rd session effect

TABLE 3. Medians´ markers in patients treated with BoNT-A and fESWT according to week of follow-up.

Week	*10MWT (seconds)*	*AS (score)*
0	28.39 *	3 **
1	17.65 *	1 **
2	15.21	1
7	17.22	1
17	12.15	1
25	12	1

(*) The difference in the 10MWT between weeks 0 and 1 was statistically significant (p= 0.004).

(**) The difference in spasticity (AS) between weeks 0 and 1 was statistically significant (p< 0.001).

TABLE 4. Medians of AS by week of follow-up and treatment.

Week	***BoNT-A***	***BoNT-A+fESWT***
0	3	3
5	2	1
17	3	1