Palestrica of the third millennium – Civilization and Sport
Vol. 19, no. 2, April-June 2018, 86–91

Effects of botulinum toxin type A on spasticity and hand function

Efectele toxinei botulinice tip A asupra spasticității și funcției mâinii

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Abstract

Background. Spasticity is well known as one of the most common after stroke complications, providing a series of negative effects including decreased range of motion, muscle spasm, different levels of contracture, local pain in the affected area.

Aims. Clinical-functional evaluation of the short and medium term effect of ultrasonographically guided injections with botulinum toxin type A (TxB-A) on the spasticity of the upper limb in post-stroke patients and the quantification of effects on international scales of spasticity and functionality.

Methods. The groups studied were composed of 60 patients, which were divided based on the doses provided in each muscle of the hand and wrist flexors (250 IU versus 333 IU). Every patient received a total dose of 1000 IU of TxB-A. The parameters that were assessed were: Modified Ashworth Scale (MAS) and Activities of Daily Living Scale (ADL), international scales for spasticity and functionality. The moments evaluated were: T0 (the initial time – injection time), T1 (one month after the injection) and T2 (3 months from T0 or 2 months from T1).

Results. Evaluation of MAS and ADL scales from T0 to T1 and T2 for the 250 IU group shows great improvements at T1 on both scales, MAS (<0.001) and ADL (<0.001), while maintaining the efficacy at T2, MAS (p-value 0.214), ADL (p-value 0.166). Evaluation of MAS and ADL scales from T0 to T1 and T2 for the 333 IU group also shows effective improvements on both scales at T1, MAS (<0.001), ADL (<0.001), and T2, MAS (0.849), ADL (0.013). Correlations between the two groups, 250 IU vs 333 IU, performed for each of the scales used in the study evidenced better results at T1 in favor of the 333 IU group on both MAS (p-value 0.034) and ADL score (p-value 0.078), with the proportion maintained in favor of the 333 IU group at T2, MAS (p-value 0.024), ADL (p-value 0.035).

Conclusions. a) TxB-A is efficient as a prime line treatment for spasticity, helping the patients in the muscle neurorehabilitation effort; b) TxB A is effective in reducing spastic muscle tone (MAS); c) TxB A is a useful asset in managing hand function (ADL).

Keywords: spasticity, botulinum toxin type A, muscle neurorehabilitation exercise

Rezumat

Premize. Spasticitatea este bine cunoscută ca fiind una dintre cele mai frecvente complicații ale accidentului vascular cerebral, având o serie de efecte negative care includ scăderea amplitudinii de mișcare, spasme musculare, contracturi de diferite intensități, dureri în zona afectată.

Obiective. Evaluarea clinică şi funcțională a efectului infiltraţiilor ghidate ecografic cu toxina botulinică tip A (TxB-A) în spasticitatea membrului superior la pacienți cu status post accident vascular cerebral și cuantificarea efectelor pe scale internaționale de spasticitate și funcționalitate.

Metode. Lotul studiat a cuprins 60 de pacienți, care au fost împărțiți în 2 loturi, în funcție de doza administrată în fiecare mușchi flexor al pumnului şi al degetelor (250 UI şi 333 UI). Fiecare pacient a primit o doză totală de 1000 UI de toxină botulinică de tip A. Parametrii evaluați au fost: Modified Ashworth Scale (MAS) și Activities of Daily Living Scale (ADL), scale internaționale pentru spasticitate și funcționalitate. Momentele evaluate au fost: T0 (timpul inițial - timpul de injectare), T1 (o lună după injectare) și T2 (3 luni de la T0 sau 2 luni de la T1).

Rezultate. Evaluarea efectelor TxB-A pe scalele MAS şi ADL de la T0 la T1 şi T2 pentru lotul cu 250 UI prezintă îmbunătățiri semnificative la T1 pe ambele scale MAS (<0,001), ADL (<0,001), menținând eficacitatea la T2, MAS (valoare p 0,214), ADL (valoare p 0,166). Evaluarea efectului pe scalele MAS şi ADL de la T0 la T1 şi T2 pentru lotul 333 UI arată, de asemenea, îmbunătățiri semnificative pe ambele scale la T1, MAS (<0,001), ADL (<0,001) şi T2, MAS (0,849), ADL (0,013). Corelațiile dintre cele două loturi, 250 UI vs 333 UI, efectuate pentru fiecare dintre scalele utilizate în studiu, prezintă rezultate mai bune la T1 în favoarea lotului 333 UI, atât pe MAS (valoare p 0,034), cât şi pe scorul ADL (valoare p 0,078), cu proporția menținută în favoarea grupului 333 UI la T2, MAS (valoare p 0,024) ADL (valoare p 0,035).

Received: 2018, April 6; *Accepted for publication:* 2018, April 28
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https://doi.org/10.26659/pm3.2018.19.2.86

Concluzii. a) TxB-A este un tratament de primă linie pentru spasticitate, ajutând pacienţii în efortul de neuroreabilitare musculară; b) TxB-A este eficientă în reducerea rezistenţei muşchiului spastic la mişcarea pasivă (MAS); TxB-A este o metodă terapeutică utilă în ameliorarea funcționalității mâinii (ADL).

Cuvinte cheie: spasticitate, toxina botulinică tip A, efort de neuroreabilitare musculară

Introduction

Spasticity is well known as one of the most common after-stroke complications (Liu et al., 2018). Lance in 1980 defined spasticity as a motor disorder 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 (Lance, 1980).

Spasticity has a series of negative effects on the affected subjects, including decreased range of motion of the upper or lower limbs, muscle spasm, different levels of contracture, local pain in the affected area (Thibaut et al., 2013; Gracies et al., 2010).

Decreasing spasticity is a hard task and not always an objective in the rehabilitation program. In some functional activities such as transfers, standing and walking, increased muscle tone is a facilitating positive sign of spasticity (O'Sullivan & Schmitz, 2016; Brashear & Elovic, 2015).

Despite being often used in managing spasticity, oral drugs offer a systemic treatment with relative benefit, and side effects are commonly dose limiting (Tickner et al., 2012).

Most studies reveal chemodenervation injections with botulinum toxin type A (TxB-A) as a first line treatment providing local action within a muscle or muscle group (Gracies et al., 2015), with very few cases of reported adverse effects (Rosales et al., 2012).

Ultrasound, electrical stimulation (ES), electromyography (EMG) and anatomic landmarks are different techniques of guidance when injecting TxB-A, with a wide range of studies evaluating their efficiency on functionality (Simpson et al., 2017; Walker et al., 2015).

Musculoskeletal ultrasound is a non-invasive, non-irradiating imaging method, repeatable whenever it is needed. It is performed in real time and provides complex morphological and hemodynamic information on musculoskeletal structures: muscles, tendons, joints (Bianchi & Martinoli, 2007).

Objectives

a) Improvements of muscle resistance to passive movement on MAS

b) Improvements of hand function in ADL

c) Correlation between reducing muscle resistance to passive movement and hand function

Hypothesis

Taking into consideration previous spasticity treatments with TxB-A with different guidance methods, US, ES, EMG, anatomical landmarks, we aimed to evaluate the efficiency of ultrasound guided TxB-A in the wrist and finger flexors in reducing muscle resistance to passive movement and improving hand function in order to reduce muscle neurorehabilitation exercise.

Material and method

a) Period and place of the research

The interventional observational study was performed in the Rehabilitation Department of the "Elias" Emergency University Hospital between September 2017 - March 2018. The study was approved by the Ethics Committee of the "Elias" Emergency University Hospital (08.08.2017), according to the Good Practice Guidelines. The patients who participated in the study gave their consent to the use and publication of the results for research purposes.

b) Subjects and groups

The studied groups were composed of 60 patients who presented upper limb spasticity within 12 months of stroke, which were divided based on the doses injected in the wrist and finger flexors (250 IU versus 333 IU). Patients having received 250 IU were injected in 4 muscles, while those having received 333 IU were injected in 3 muscles. All patients received a total TxB-A dose of 1000 IU. The target muscles were pronator teres, flexor carpi radialis, flexor carpi ulnaris, flexor digitorum superficialis, flexor digitorum profundus, flexor pollicis longus.

c) Tests applied

The following parameters were assessed: the Modified Ashworth Scale (MAS) and the Activities of Daily Living (ADL) Scale. MAS is an international tool which measures spasticity on a scale between 0 and 4, where 0 indicates the absence of spasticity and 4 indicates maximum intensity, meaning that the limb is fixed in flexion or extension. The ADL Scale is an 11-item scale which includes presumed personal care activities: bath and shower; bladder and gut function management; dressing; eating; food supply; functional mobility; maintaining one's own helping device; hygiene and personal care; sexual activity; rest and sleep; toilet hygiene.

d) Statistical processing

The tests applied are described in Table I. It should be mentioned that most of the data are of scale type (this is the name as per the SPSS Statistics v22 tool used), but also ordinal. However, the comparison test type is the same, meaning that the tests below should be used when data are at least ordinal.

Table I

Tests used according to the data type and distribution

Comparison type/data	Distribution	Comparison test used
Independent	Normal	Independent t-test
Independent	Non-normal	Mann-Whitney U test
Paired	Normal	Paired t-test
Paired	Non-normal	Wilcoxon matched paired test

The values used as reference were means whenever the distribution was normal for both data samples, or medians whenever at least one sample was not normally distributed. Mention: this is in fact what the comparison test is assessing.

All patients were evaluated at the initial time T0, which is the time where the ultrasound guided injections were performed after evaluating the patients for the target muscles. Spasticity was assessed using MAS and hand function was evaluated on the ADL Scale. The next evaluations were performed at one month (T1) and three months (T2) after the injection, to quantify the effect of the injections on the same evaluation scales (MAS, ADL).

Although spasticity has some common patterns for the upper limb after stroke, it can occur in any muscle, so that we chose the target muscles for each patient. Flexor muscles were evaluated individually and we noted a mean muscle spasticity value on MAS for each patient (e.g.: 1 patient; 333 IU group; spasticity of the flexor carpi ulnaris = 3 MAS; flexor digitorum profundus = 4 MAS; flexor pollicis longus = 3 MAS; average MAS of the patient = 3.33 MAS).

For the hand function we used the ADL Scale, an 11-item scale where we counted the activities that a person performs at the evaluation time (e.g.: eating, sleeping, clothing. ADL score = 3).

Apart from this perspective of comparing the 2 groups of patients (250 IU versus 333 IU), which was used as a criterion for independent comparisons, we also compared patients using paired-sample criteria: the same group was assessed from one period to another (T0-T1-T2) in order to evaluate the extent to which the injections improved the parameters.

Results

The results are presented in Tables II-XV.

Since the paper aims to show the effects of post stroke spasticity improvement based on the injected TxB-A dose, we first need to demonstrate that initially (at T0), the dose-based groups were homogeneous (Table II).

We compared the patients at T1 (one month after injection, in absolute values), as the T0 measurement was performed to validate patient homogeneity. Then, we compared them at T2 (3 months after the injection).

At T1, in absolute values, it can be seen that one month after the injection there were significant differences between the two groups (Table III).

Thus, if at T1, in absolute values, the group that received 250 IU had a better score than the other group, from 1.92 to 1.63 on the Ashworth scale, in terms of percentage change (as percent increase / decrease at T1 compared to T0), this difference was not considered relevant; the average decrease of 36 percentage points (250 IU) compared to 43 (333 IU) was not significant.

At T2, in absolute values, significant differences were observed between the two groups formed depending on the dose received 3 months after the first injection. If those who received 250 IU had an average Ashworth score of 1.98, those who received 333 IU had an average score of 1.6. The difference in the median (we remind that the median is a statistically more relevant indicator for non-normal distributions, as is the case with one of the two groups) is even more visible (Table IV).

a) 250 IU group

Thus, one month after the first injection, a significant difference was found (with a p-value that is well below 0.05), which shows that injection itself is relevant (Table V).

It can be seen that there are no significant differences between one month and three months. The table above shows that the improved scale has, on average, almost the same value for both periods (Table VI).

b) 333 IU group

For the 333 IU group, we first found that Ashworth's decrease was statistically significant from T0 to T1.

It can be seen that similarly to the 250 IU group, the 333 IU group had an improvement without significant differences one month after the first injection compared to 3 months. This shows that the effect was important at 1 month, after which it was maintained for the next 2 months (Tables VII, VIII).

Table II

Statistical comparison of Ashworth at T0 based on the dose

T0: MAS	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
250 IU group	30	3	3	0.29	No	Mann-Whitney U	0.092
333 IU group	30	2.87	3	0.27	No		

Table III

Statistical comparison of Ashworth at T1 based on the dose

T1: MAS	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
250 IU group	30	1.92	1.88	0.5	Yes	Mann-Whitney U	0.034
333 IU group	30	1.63	1.66	0.58	No		

Table IV

Statistical comparison of Ashworth at T2 based on the dose

T2: MAS	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
250 IU group	30	1.98	2	0.58	Yes	Mann-Whitney U	0.024
333 IU group	30	1.6	1.33	0.64	No		

Table V

Statistical comparison of Ashworth between T0 and T1 for 250 IU

MAS	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
T0	30	3.01	3	0.29	No	Wilcoxon Matched paired	<0.001
T1	30	1.93	1.88	0.5	Yes		

It can be observed that both groups had improvements at 1 month and 3 months, and although there were slightly higher averages in the 333 IU group, statistically speaking the difference was not relevant between the groups (Tables X, XI, XII, XII, XIV, XV).

Table VI
Statistical comparison of Ashworth between T1 and T2 for 250 IU

MAS	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
T1	30	1.93	1.88	0.5	Yes	Paired t-test	0.214
T2	30	1.98	2	0.58	Yes		

Table VII
Statistical comparison of Ashworth between T0 and T1 for 333 IU

MAS	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
T0	30	2.88	3	0.27	No	Wilcoxon matched paired	<0.001
T1	30	1.63	1.66	0.58	No		

Table VIII
Statistical comparison of Ashworth between T1 and T2 for 333 IU

MAS	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
T1	30	1.63	1.66	0.58	No	Wilcoxon matched paired	0.849
T2	30	1.6	1.33	0.64	No		

Table IX
Statistical comparison of ADL at T0 based on the dose

T0: ADL	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
250 IU group	30	3.27	3	1.413	No	Mann-Whitney U	0.059
333 IU group	30	3.87	4	1.252	No		

Table X
Statistical comparison of ADL at T1 based on the dose

T1: ADL	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
250 IU group	30	5.23	5	2.285	Yes	Mann-Whitney U	0.078
333 IU group	30	6.47	7	2.751	No		

Table XI
Statistical comparison of ADL at T2 based on the dose

T2: ADL	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
250 IU group	30	5.4	5	2.298	No	Mann-Whitney U	0.031
333 IU group	30	7.03	7	3.034	Yes		

Table XII
Statistical comparison of ADL at T0 and T1 for 250 IU

ADL	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
T0	30	3.27	3	1.413	No	Mann-Whitney U	<0.001
T1	30	5.23	5	2.285	Yes		

Table XIII
Statistical comparison of ADL between T1 and T2 for 250 IU

ADL	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
T1	30	5.23	5	2.285	Yes	Mann-Whitney U	0.166
T2	30	5.40	5	2.298	No		

Table XIV
Statistical comparison of ADL between T0 and T1 for 333 IU

ADL	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
T0	30	3.87	4	1.252	No	Wilcoxon matched paired	<0.001
T1	30	6.47	7	2.751	No		

Table XV
Statistical comparison of ADL between T1 and T2 for 333 IU

ADL	N	Average	Median	Standard deviation	Normal distribution?	Comparative test	p
T1	30	6.47	7	2.751	No	Wilcoxon matched paired	0.013
T2	30	7.03	7	3.034	No		

Discussions

During the measurements, a technical disadvantage was observed in the fact that the dose was administered to different muscles (6) and given the low number of patients (60), the average muscle spasticity was used instead of scoring each of the six separate muscles. This of course opens the perspective of a future investigation given the significant results mentioned above.

All of our patients in the study received concomitant neurorehabilitation therapy, going from passive stretching to functional electrical stimulation. This is recommended by current guidelines in the treatment of upper limb spasticity, using TxB-A injections with concomitant therapies (Wissel et al., 2009).

The Ashworth scale for both the 250 IU and the 333 IU groups evidences a signifiant improvement 1 month after injection with the maintenance of the improvements 3 months after the injection. The ADL score has a minimal improvement at 1 month and a significant improvement at 3 months. This shows that after 1 month, when TxB-A was effective in reducing spastic muscle tone, the patients were able to exercise at a better intensity in order to improve hand function and the results were seen at 3 months.

For both 250 IU and 333 IU, there was a significant improvement at T1, showing that TxB-A is effective in reducing muscle resistance to passive movement, with a slight advantage on the Ashworth scale for the 333 IU group.

As the results of our study suggest, in an article published in February 2015, Andrea Santamato reviewed the use of higher TxB-A doses and showed that these were effective in reducing upper or lower limb spasticity after stroke (Santamato et al., 2015).

It can be seen that similarly to the 250 IU group, the 333 IU group had an improvement without significant differences one month after the first injection compared to 3 months. This shows that the effect is important at 1 month, after which it is maintained during the next 2 months. This can lead us to the idea of further studies to analyze the possibility of extending the period of injection to more than 3 months and to reevaluate the time lasting effect of TxB-A.

All patients in our study were within 1 year of stroke, and guidelines do not offer a time limit beyond which TxB-A may be considered ineffective in reducing symptoms (Fheodoroff et al., 2015).

A recent meta-analysis of 10 clinical trials using TxB-A shows global benefits in reducing upper limb spasticity after stroke in adults (Foley et al., 2013).

It has been demonstrated that early TxB-A injections after stroke (2-12 weeks) can induce important improvements in upper limb spasticity (Rosales et al., 2012) and also ameliorate arm function (Cousins et al., 2010). Current guidelines also show the possible advantages of early treatment with TxB-A in upper limb spasticity (***, 2013).

This leads us to conduct further studies on a higher number of patients, while beginning the therapy at an earlier stage after stroke.

Conclusions

1. TxB-A is a prime line treatment for spasticity, helping patients in the muscle neurorehabilitation effort; as shown in the study, patients had a better hand function on the ADL scale at 3 months, after TxB-A became effective, and they could exercise better.

2. TxB-A is effective in reducing muscle resistance to passive movement on MAS at 1 month after injection, with the maintenance of the effect at three months.

3. TxB-A is a useful asset in managing hand function, as shown on the ADL scale at 3 months after the injection for both groups (250 IU and 333 IU).

4. Further studies should be conducted in the future to establish the optimum dose-effect management of spastic muscles and the injection intervals.

Conflicts of interest

Nothing to declare.

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