Original paper

Folia Neuropathologica

Botulinum neurotoxin-A in a patient with post-stroke spasticity: a neurophysiological study

Safa Muntadher Fawzi[1], Farqad Bader Hamdan[1], Israa F. Jaafar[2], Gheyath Abd Ali Shallal Al Gawwam[3]

[1]Department of Physiology, College of Medicine, Al-Nahrain University, Baghdad, Iraq, [2]Department of Dentistry, Al-Esraa University College, Baghdad, Iraq, [3]Department of Medicine, College of Medicine, Baghdad University, Baghdad, Iraq

Folia Neuropathol 2023; 61 (4): 412-418

DOI: https://doi.org/10.5114/fn.2023.130030

Abstract

Introduction: *Post-stroke spasticity (PSS) is a disorder of the sensory-motor control, leading to upper motor neuron lesions manifesting either as intermittent or sustained involuntary activation of muscles. Botulinum neurotoxin-A (BoNT-A) is mostly utilized in a variety of therapeutic indications, and it is effective and safe in the management of focal PSS in the rehabilitation scenario. The study aimed to evaluate the effect of BoNT-A administration on H-reflex of upper and lower limbs following PSS. In addition, the investigation of the association among the degree of spasticity (assessed by the Modified Ashworth Scale [MAS]) and motor neuron pool excitability (assessed by analysing H-reflex excitability) was done.*

Material and methods: *Fifty patients with a stroke of either sex aged 30 to 60 years presented with either upper or lower limb focal spasticity were studied. BoNT-A was given on two occasions to the gastrocnemius, soleus, biceps brachii muscles and flexor carpi radialis (FCR). H-reflex was documented from the FCR and soleus muscles at baseline and 3-4 weeks post BoNT-A injection. Medical Research Council scale and MAS were used to assess the PSS and muscle strength.*

Results: *H-reflex latency and amplitude, H/M ratio recorded from FCR and soleus muscles were significantly different between pre- and post-management. The MRC scale was significantly increased whereas the MAS was significantly reduced post BoNT-A injection.*

Conclusions: *BoNT-A causes obvious improvement in PSS clinically as assessed by MAS and MRC scale as well as neurophysiologically by H-reflex. A negative correlation between H-reflex latency but not the amplitude or H_{max}/M_{max} ratio and MAS was observed.*

Key words: *stroke, spasticity, H-reflex, BoNT-A.*

Introduction

The stroke is a leading cause of mortality and morbidity in adult survivors [7]. Spasticity is a common condition, but not an inevitable sequela in cases with stroke. The prevalence is 30% to 80% and the incidence is between 27% at 4 weeks and 34% at 1,5 year [7,39].

Post stroke spasticity (PSS) is manifested by pain, joint contracture and stiffness. It may result in an abnormal limb posture, lower quality of life, raised management cost, and elevated caregiver burden [4]. Joint range permanent loss has been recorded to occur within 3 to 6 weeks [30]. Post stroke spasticity is noticed more in the flexor muscles of the upper limbs and extensor muscles of the lower limbs. In a decreasing manner, PSS developed in 79% of the elbow, 66% of the wrist and ankle, and 58% of shoulder [52]. Further, it was found more in the upper extremities than in the lower [33,49]. Early diagnosis and treatment of PSS include complication reduction, improvement of functions and increased independency. The treatment options are physical therapies, pharmacological man-

Communicating author:

Safa Muntadher Fawzi, Department of Physiology, College of Medicine, Al-Nahrain University, Baghdad, Iraq 10047,
e-mail: salihkazim@yahoo.com

agement, phenol and botulinum neurotoxin (BoNT) neurolysis and surgical procedures [30].

Chemodenervation with botulinum neurotoxin-A (BoNT-A) injections is safe and effective management in clinical practice [14,18]. The injections decrease muscle tones and symptoms, and improve motion ranges in the upper and lower limbs [10,19]. They act on the neuromuscular junction by inhibiting the acetylcholine exocytosis from presynaptic nerve terminals [45], and by inhibiting selective reversible muscle contractions without weakness while the sedation lasts for 3-4 months [28].

The H-reflex continues to be the significant tool for studying neuro-motor controlling processes and clarifying neuro-motor deficits [5,29]. Many works revealed that spastic cases exhibit larger H-reflex amplitudes or H_{max}/M_{max} ratios than the healthy groups or their unaffected sides in the prone position [23], which suggested that the spasticity at rest was caused by the raised excitability of neurons of motor spinal circuits. H-reflex measurements are used to determine how therapeutic interventions affect reflex pathways, i.e., baclofen [46] and botulinum toxin [27].

The current study aimed to explore how H-reflex changes in survivors with PSS are enhanced by BoNT-A and to investigate the possible correlation between H-reflex changes and the Modified Ashworth Scale (MAS) and Medical Research Council (MRC) scale post BoNT-A injection.

Material and methods

Study design and setting

A randomized clinical study was conducted in the Clinical Neurophysiology Unit, Baghdad Teaching Hospital from January to July 2022.

Ethical approval

The study was approved by the College of Medicine, Al-Nahrain University (IRB#86: Date: 24/1/2022) and by the Baghdad Teaching Hospital, Medical City, Ministry of Health (#3387: Date: 23/1/2022). Each patient provided written informed consent for enrolment.

Participants

Fifty patients with first-ever stroke (haemorrhagic or ischemic) detected by computed tomography (CT) scan and having focal spasticity of ≥ 3 months were recruited and completed the study protocol. The patients were of either sex and aged 30 to 60 years. They were referred by a senior neurologist from those attending the Neurology Outpatient Clinic of Baghdad Teaching Hospital, Medical City.

Exclusion criteria

Patients with any known neurologic, neurodegenerative, orthopaedic or musculoskeletal disorder that affects the nerve conduction study, those who have contraindications to neurotoxin (e.g., sensitivity), those who receive muscle relaxant two weeks before or during the study were excluded from the study.

Procedure

All cases underwent a full clinical and neurological examination including scoring of the muscle tones at the elbow and ankle joints using the modified MAS [2] and had muscles power tested in the upper and lower extremities according to the MRC scale [9] at the first visit of patients and 3-4 weeks later.

Data measurement

H-reflex testing was done early in the morning for every patient at the first visit and 3-4 weeks later using EMG/EP machine (Medtronic Keypoint, Denmark). The temperature was maintained (25-28°C) during the testing, the temperature of the skin was 32-34°C.

H-reflex was reported from the FCR and soleus muscles. Then, an onset of latency of the M wave and H-reflex was calculated from the stimulus artifact to the first deflection from the baseline. H-reflex and M-wave amplitudes were calculated. The amplitude was calculated as peak-to-peak values. When the H-wave was present, the strength of stimuli was adjusted slowly to find H_{max} and M_{max}. The H_{max}/M_{max} ratio was measured as ratios of the maximum amplitude of both action potentials [40].

BoNT-A

All subjects with PSS were injected BoNT-A (Canitox® vials) toxin at the first and second visit. The vial contained 100 U diluted with 4 ml of normal saline [15], which was aspirated to a syringe ready to be used. The toxin doses were administered to injected limbs with 100 U/session at the first visit (baseline) and the second visit (after 3-4 weeks). Administration to the target gastrocnemius, soleus, FCR, and biceps brachii muscles was done using palpation/anatomic landmarks and according to the International Movement Disorder Society guidelines [51].

Statistical tools

The statistical tools included Microsoft Excel 2016 (Microsoft Corporation, USA) and IBM SPSS (Statistical Package for Social Sciences) version 26 (IBM Corporation, USA). Continuous pre- and post-treatment findings

Table I. Scoring of muscle strength and tone according to the MRC scale and MAS of the study population ($n = 50$)

Clinical scale	BoNT-A injection		*P*-value
	Pre-, *n* (%)	Post-, *n* (%)	
Medical Research Council (grade)			
1	4 (8)	0 (0)	0.001
2	24 (48)	1 (2)	
3	22 (44)	9 (18)	
4	0 (0)	40 (80)	
Total score	2.36 ±0.63	3.78 ±0.47	< 0.001
Modified Ashworth Scale (grade)			
1	0 (0)	5 (10)	< 0.001
2	5 (10)	32 (64)	
3	18 (36)	13 (26)	
4	26 (52)	0 (0)	
5	1 (2)	0 (0)	
Total score	3.46 ±0.71	2.16 ±0.58	< 0.001

were provided as mean and standard deviation (SD). Non-continuous variables were reported as median and range. The paired student (*t*) test and the Wilcoxon test were used. A $p < 0.05$ was considered significant.

Results

The mean age was 47.68 ±7.99 years (range = 33-60). Twenty-four (48%) patients were males and 26 (52%) were females.

Regarding the MRC scale, 24 patients scored 2, 22 scored 3, and only 4 patients scored 1. On the other hand, for the MAS, 26 patients scored 4, 18 scored 3, 5 scored 2, and only one patient scored 5. The MRC scale score was significantly increased post-treatment vs. pre-treatment values ($p < 0.001$) whereas the MAS was significantly reduced post-treatment relative to pre-treatment values ($p < 0.001$) (Table I).

Table II shows the H-reflex data of the right and left sides from the upper and lower limbs. Latency was prolonged whereas the amplitude and the H/M ratio were reduced post-BoNT-A injection as compared to the pre-treatment values.

Table II. Pre- and post-BoNT-A injection of H-reflex data

Limb	M wave		H wave		H_{max}/M_{max} ratio
	Latency (ms)	Amplitude (µV)	Latency (ms)	Amplitude (µV)	
Right upper (n = 12)					
Pre-BoNT-A	1.03 ±0.08	2.35 ±0.66	8.83 ±0.99	1.29 ±0.26	0.56 ±0.11
Post-BoNT-A	0.99 ±0.09	2.32 ±0.87	11.03 ±0.85	0.86 ±0.19	0.4 ±0.14
p-value	0.240	0.880	< 0.001	< 0.001	0.003
Left upper (n = 13)					
Pre-BoNT-A	1.00 ±0.13	2.45 (1.3-3.3)	8.52 ±0.88	1.15 (0.6-1.7)	0.50 (0.35-0.7)
Post-BoNT-A	0.99 ±0.07	2.1 (1.4-3.9)	10.28 ±0.96	0.9 (0.4-1.2)	0.37 (0.22-0.64)
p-value	0.674	0.305	< 0.001	0.002	0.005
Right lower (n = 12)					
Pre-BoNT-A	1.03 ±0.06	2.73 ±0.67	18.2 (7.3-27.1)	1.5 (0.2-2.2)	0.58 (0.06-0.75)
Post-BoNT-A	0.98 ±1.0	2.86 ±0.53	23.55 (8.9-29.4)	1.05 (0.1-1.8)	0.39 (0.04-0.56)
p-value	0.053	0.382	0.002	0.002	0.002
Left lower (n = 13)					
Pre-BoNT-A	1.0 (0.8-2)	2.8 (1.5-4.3)	18.6 (15.8-27.8)	1.6 (1.3-2.8)	0.6 (0.34-0.75)
Post-BoNT-A	1.0 (0.7-2.0)	3.0 (1.6-5.4)	23.4 (20.4-30.1)	1.1 (0.2-2.9)	0.37 (0.12-0.58)
p-value	0.190	0.033	0.001	0.001	0.001

The data are represented as mean ±SD or median and range.

Following BoNT-A injection, none of the H-reflex data was correlated with age, MAS, or MRC scale scores apart from the H-reflex latency which showed a negative correlation with MAS ($r = -0.286$, $p = 0.044$) (Table III and Figure 1).

There was no association found between the H-reflex data and gender as demonstrated in Table IV.

Discussion

BoNT effects on the quantification of the muscle strength and spasticity

In our study, BoNT injections had the ability to successfully decrease spasticity of the paretic side.

Table III. Correlation of H-reflex data with age, MRC, and MAS post-treatment with BoNT-A

Variable	Significance	Age (years)	MRC	MAS
M latency (ms)	*r*	0.160	–0.148	–0.197
	p	0.267	0.306	0.170
M amplitude (µV)	*r*	0.055	–0.013	–0.264
	p	0.703	0.929	0.064
H latency (ms)	*r*	–0.171	0.170	–0.286
	p	0.235	0.237	0.044
H amplitude (µV)	*r*	0.123	0.117	–0.154
	p	0.395	0.418	0.287
H_{max}/M_{max} ratio	*r*	0.276	0.155	–0.011
	p	0.052	0.283	0.937

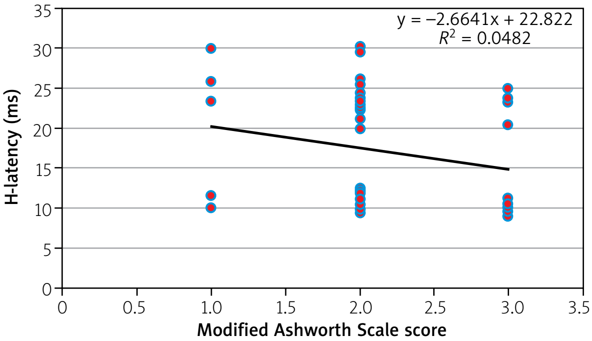

Fig. 1. Relationship between H-latency and MAS.

The MAS scores were dropped in all patients to a variable degree indicating that the doses of BoNT may be adequate for these cases. This finding harmonizes with that of other researchers and meta-analyses [1,8,32]. BoNT exerts its effects by inhibiting acetylcholine releasing at the neuromuscular junction by complex processes by inducing locally-confined neuromuscular blocking development, resulting in the paresis of the targeted spastic muscles, thus the spasticity is then reduced [25,43].

This study also demonstrates a significant increase in cumulative MRC score at visit 2 after BoNT-A injection denoting increased muscle strength. This aligns the findings with other studies [42,44].

Spasticity is a positive upper neuro-motor sign present as excessive muscle tones and stretch reflexes, while weakness and lower muscle strength were a negative upper neuro-motor sign [34]. These consequences emerging, evolving, and interacting with each other lead to the traditional clinical manifestation during the recovery phase beyond the stroke [20,21]. Consequently, spasticity and weakness usually result in the immobilization of the joint when shortened of muscle length, which potentiates the contracture, which then exacerbates spasticity of muscles. This vicious cycle continues

Table IV. Association between gender and H and M waves data

Variable	Male (*n* = 24)	Female (*n* = 26)	*p*-value
M latency (ms)			
Mean ±SD	0.99 ±0.1	1.02 ±0.21	0.503
Range	0.7-1.2	0.8-2.0	
M amplitude (µV)			
Mean ±SD	2.68 ±0.95	2.62 ±0.92	0.822
Range	1.5-5.4	1.4-5.0	
H latency (ms)			
Mean ±SD	17.24 ±8.1 1	16.91 ±6.15	0.946
Median	11.25	16.2	
Range	8.9-30.1	9.1-25.3	
H amplitude (µV)			
Mean ±SD	0.90 ±0.34	1.08 ±0.54	0.238
Median	0.9	1.0	
Range	0.1-1.7	0.2-1.9	
H_{max}/M_{max} ratio			
Mean ±SD	0.34 ±0.12	0.41 ±0.16	0.084
Median	0.37	0.44	
Range	0.04-0.56	0.12-0.73	

and worsens the condition if there is no effective interruption [20,21,38].

In the voluntary control, the improvement of spastic muscles occurs from decreased reciprocal inhibitions from the antagonistic muscle post injection. Previously, data have shown that administration of BoNT injections can paralyze afferent fibres [16], in addition to the acetylcholine release blocking presynaptically in the neuromuscular junctions, thus resulting in the drop in the inhibition from paralyzed flexor muscles post injections.

The increment in the muscle strength and simultaneous decrement in spasticity as assessed by MRC scale and MAC, respectively, after BoNT-A injection were of value for those patients with PSS.

BoNT effects on H-reflex

Significantly, the H_{max}/M_{max} values are greater in the spastic limbs prior to BoNT-A injection due to elevation of motoneuron pool excitability in the stroke cases [41]. Following BoNT-A injection, the amplitude and H_{max}/M_{max} ratios were lowered at the spastic limb of stroke patients. This suggests a decrease in the motoneuron pool excitability. As it was known, H-reflex represents a single synapse reflex which is used to evaluate the functional conditions of the spinal reflex loops and has been employed in the evaluation of spinal excitability [24,47].

Patho-physiologically, the mechanism of spasticity post stroke is still being explored and it is a complicated condition. Currently, authors believe that the reason for stretch reflex hyper-excitability in subjects with PSS is initially because of abnormal remodelling of the pathway of the descending conduction upon the spinal cord levels and the error processing within these levels [48]. All these changes might affect the excitability of alpha motor neurons [31].

The alpha motor neuron excitability might represent the spasticity severity to some extent. However, H-reflex is reflecting the alpha motor neuron excitability, which is used to detect the peripheral sensory afferent roles or supra-spinal descending conduction pathways in various aspects of man motions [6].

Patients with PSS exhibited shorter latency of H-reflex. This harmonizes with the observation of other investigators [3,26]. With BoNT-A injection, our results clarified prolongation in the H-reflex latency.

Here, a negative correlation was reported between latency of H-reflex and MAS after BoNT-A injection. This correlation will enhance the H-reflex validity and MAS as a neurophysiological and clinical method for assessing spasticity of muscles. The absent correlation between MAS and H_{max}/M_{max} could be due to the fact that the latter reached its maximum in 8-24 weeks and can be noted shortly post the spinal cord injuries [22]. Importantly, cases should be examined after six months of the onset of the disease, which is inversely seen in this study.

Previously, neurophysiological researches on post-stroke spasticity focused on individuals who had a stroke in the chronic phase [17,36,41]. That is when the spasticity starts as abnormal neuroplasticity developments, and when the median time to spasticity detection is one month post the onset of the stroke [37]. An early spasticity identification is crucial for adequate management and better prognosis. In parallel with the neurophysiological findings, recently a meta-analysis study has suggested that spasticity appeared or disappeared within one to three months post stroke and rested stable after three months [53].

There are several factors accounting for the absent association between the H_{max}/M_{max} ratios and the MAS scores. Firstly, authors concluded that the F wave represented a more sensitive marker of neurophysiology of the spasticity than the H-reflex [26,35]. Here, this study did not report the F wave, because of the activity of a very small percent of the alpha neuro-motor population accounting for the F wave occurrence [13].

Secondly, the mechanisms of neurophysiology that underlie include changes in the excitability of the interneurons of the spine as well as the alpha motor neuron [12]. Thus, it is notable to undertake a study of the association among the spinal segmental circuitry changes and spasticity of muscles recording as flexor reflex. Recently, a study dealt with the neurophysiological changes evolution in the segmental circuitry of the spine, and showed that the flexor reflexes amplitude may fall when the spasticity is established [22].

Lastly, a poor relationship between the findings of the tests of neurophysiology and the spasticity degrees may also occur due to problems with introducing of the MAS itself. The scale relies on the subjective judgment of the examiner and calculates the resistance of the passive muscles stretching. The resistance usually reflects a combination among spasticity, fixed muscle contractures and thixotropy [11,50]. By exclusion, in this study we carefully chose cases which were clinically diagnosed with fixed contractures, hence, it is not possible to be certain that these changes in the fibre structures or the viscoelastic features of muscles did not appear.

The limitations that required addressing are as follows. This study investigated the relationship among MAS and H-reflex. The number of patients within each group was insufficient. A larger sample size is needed to validate the neurophysiological parameters. We did not follow the patients for a longer period to check for the effect of BoNT-A on MAS and H-reflex in those with chronic PSS. The other limitation is the difficulty in reaching the hospital for patients who complained of post-stroke spasticity. There are several patients who refused injection, whereas others received only one injection at the first visit. Patients' loss of follow-up after four weeks led to a limited number of patients.

It is a well-known fact that BoNT-A inhibits the release of acetylcholine (ACh) from presynaptic motor neurons. BoNT-A invades nerve cells where it releases an enzyme preventing muscle contraction called SNARES which forms a complex between the nerve and muscle cell.

There is up regulation of ACh receptors after 2 to 3 weeks of injection. That is why the injection was repeated after this period. ACh receptors' increase is caused by up regulation. This was a clinical study on the effect of BoNT-A on spastic patients and aimed to look for clinical improvement and changes in H-reflex.

Medically patients had clinical improvement regarding decreased spasticity, better functional outcome regarding movement of upper and lower limbs, decreased complication of spasticity like abnormal posture and increased independency of patients.

Conclusions

Evidently the BoNT injection can decrease spasticity. There is a statistical association existing in the latency, amplitude, and H_{max}/M_{max} ratio of the H-reflex within hemiplegic stroke cases pre- and post-BoNT-A injection. We hope that this work will contribute to the provision of an effective BoNT-A injection for treatment of PSS in hemiplegic subjects.

Disclosure

The authors report no conflict of interest.

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