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Botulinum toxin-A injection improves motor recovery in patients with stroke

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Abstract

Aim: Spasticity that occurs after a stroke may contribute to disability. Botulinum toxin type-A (BTX-A) injections are commonly used to manage spasticity. This study sought to determine the effectiveness of BTX-A injections on spasticity and motor recovery in patients with stroke.

Materials and Methods: Twenty-five patients with stroke scheduled for BTX-A injection for spasticity were included in the study. The patients were analyzed in two groups: upper limb and lower limb group. A single dose of BTX-A was applied to the patients. Before, 2, and 12 weeks after BTX-A injections, motor function was assessed using Brunnstrom recovery stages, and spasticity was evaluated according to Modified Ashworth Scale (MAS). The lower limb group additionally underwent the Functional Ambulation Classification (FAC) and 10-meter walking test.

Results: Mean age of patients was 54.96 ± 12.84 years. Eighteen patients were enrolled in the upper limb group and 23 in the lower limb group. Clinical evaluation of the upper limb group two weeks after injections demonstrated a significant decrease in shoulder adductor muscle MAS, elbow, wrist, and finger flexor muscles MAS, and a significant improvement in Brunnstrom recovery stages for the upper limb and hand ($p<0.05$). At week 12, spasticity decreased only for the shoulder adductor muscles. In the lower limb group, clinical evaluation at week 2 showed a decrease in the knee extensor and toe flexor muscles MAS. Assessment of the patients at week 12 found a significant improvement in Brunnstrom recovery stage for the lower limbs ($p<0.05$). There was no statistically significant recovery in the FAC and 10-meter walking test ($p>0.05$).

Conclusion: This study supports that BTX-A injections are effective for improving spasticity and motor function in patients with stroke.

Introduction

Stroke is a major cause of death and disability worldwide, and spasticity is one of the factors contributing to disability after stroke [1]. It was reported that the incidence of spasticity is 39.5%, and the prevalence of severe spasticity [Modified Ashworth Scale (MAS) $\geq$ 3] is 9.4% in patients with paresis and first-ever stroke [2].

While spasticity can have positive effects such as assisting trunk stability and standing, it can also lead to problems such as joint contractur and impaired walking and balance [3]. In addition, spasticity may also interfere with motor control and learning in stroke patients [4].

Treatment of spasticity primarily aims to provide functional improvement and should be conducted multidisciplinary. Many treatment options are available, including eliminating the causes of spasticity, physical therapy, medical treatment (systemic or regional), and surgery (intrathecal, orthopaedic, or neurosurgical). One of these options is to use botulinum toxin type A (BTX-A) injections, which have been proven effective and well-tolerated in treating focal upper and lower limb spasticity [5,6]. BTX-A injections are also commonly used as they have fewer side effects than oral antispasticity drugs and are less invasive than surgical treatments. Although BTX-A has not been proven to recover motor function, it has been reported to have beneficial effects on upper limb function and mobility treating post-stroke spasticity. The present study aimed to determine the effect of BTX-A injection on spasticity and motor recovery in patients with stroke.

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Materials and Methods

Twenty-five patients with stroke enrolled on the study between March 2019 and August 2019. Inclusion criteria were: having a stroke duration of at least three months and having a MAS score of 1+ or higher for spasticity in the upper and/or lower limbs.

Exclusion criteria were; having any central nervous system disease other than stroke, being uncooperative, being nonambulatory, having a history of bilateral stroke, history of fracture of upper or lower extremity on the affected side, having surgery for joint or joint contracture, having pregnancy or lactation, being hypersensitive to BTX-A injections and history of dose changing of antispasticity medication in the last three months.

Initially, 30 patients with stroke were enrolled for assessment. One patient died, one patient had a new cerebrovascular event, and three did not attend follow-ups at 2 and 12 weeks and thus could not complete the study. Twenty-five patients were included in the study. The patients were analyzed in upper and lower limb groups based on the muscles that received BTX-A injections. Eighteen patients were included in the upper extremity group, and 23 in the lower extremity group. Sixteen patients were assessed for both upper and lower limb groups (Figure 1). Patients underwent examinations to identify muscles that would receive BTX-A injections. One vial (100 IU) of BTX-A (Botox®, Allergan) was reconstituted with 2 ml of normal saline. BTX-A injections were administered by the same physical therapy and rehabilitation specialist under ultrasound guidance. After injection, patients were prescribed a home-based training program consisting of exercises for improving the range of motion of the limbs, strengthening, and balance for 30 minutes a day, five days a week.

Before and at 2 and 12 weeks after receiving BTX-A injections, patients were evaluated for motor functions using Brunnstrom recovery stages and spasticity using the Modified Ashworth Scale (MAS). The lower limb group was evaluated using the functional ambulation classification (FAC) and 10-meter walking test (10-mwt). The same specialist performed all evaluations.

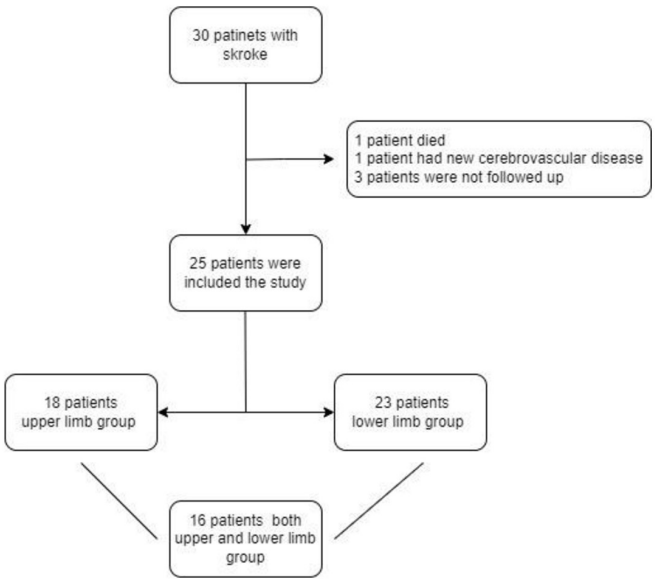

Figure 1. Study flowchart In the figure, please correct patinets with patients.

Brunnstrom recovery stages classify motor recovery in hand, upper limbs, and lower limbs into six stages [7]. The test defines the sequence of motor recovery after stroke depending on the spasticity, synergy, and voluntary movement [8]. Higher values show better motor improvement.

The MAS is a commonly used and easy-to-administer instrument for assessing spasticity. It is an ordinal scale that evaluates muscle tone with a grade score of 0, 1, 1+, 2, 3, or 4. A score of 0 means no spasticity and 4 means severe spasticity. In the present study, MAS scores of 1+, 2, 3, and 4 were converted into 2, 3, 4, and 5 for statistical analysis [9-11].

In the 10-mwt, patients were asked to walk 10 meters on flat ground with or without assistance, and walking time was noted [12]. FAC is a scale that assesses patients' ambulation ability using six categories rated from 0 to 5. A score of 0 indicates being nonambulatory, and 5 indicates complete independence in ambulation [13].

All patients were informed about the study, and a consent form was obtained. The 1975 Declaration of Helsinki performed all procedures. The study was approved by the Local Institutional Clinical Research Ethics Committee (University of Health Sciences Fatih Sultan Mehmet Education and Research Hospital Clinical Research Ethics Committee, FSM EAH - KAEK 2019/19).

Statistical analysis

The power analysis was calculated according to a previous study by Demiryurek et al. [14]. For ankle MAS, the sample size determined for effect size d: 1.859, standard deviation 0.62, Power:0.90 and α:0.05 was determined as minimum n=6 patients. This calculation was performed using G*Power version 3.0.10 software.

Statistical analyses were performed using the IBM SPSS Statistics 22 software package (IBM Turk Limited Company, Istanbul, Turkey). Normal distribution was assessed using the Shapiro-Wilk test. Wilcoxon Signed Ranks test was used to compare quantitative data for in-group comparisons of parameters that did not show normal distribution. Statistical significance was accepted at the $p<0.05$ level.

Results

The mean age of 25 patients who completed the study was 54.96 ± 12.84 years. The general characteristics of the patients are shown in Table 1. Muscles of the upper and lower limbs that received BTX-A injections and doses are shown in Table 2.

In the upper limb group, there was a statistically significant improvement in shoulder adductor, elbow flexor, wrist flexor and finger flexor muscles MAS at week 2. However, assessment at week 12 showed a statistically significant improvement in the MAS score only for the shoulder adductor spasticity ($p<0.05$). Assessment with Brunnstrom recovery stages showed statistically significant progress in the upper limb and hand at week 2 ($p<0.05$) but no statistically significant improvement in the upper limb and

hand compared to the baseline examination at week 12 ($p>0.05$) (Table 3).

In the lower limb group, there was a statistically significant decrease in the knee extensor and toe flexor muscles' MAS scores at week 2 ($p<0.05$). However, there was no statistically significant decrease in the ankle plantar flexor muscle MAS scores ($p>0.05$). Assessment at week 12 found no significant difference in the knee extensor, ankle flexor, and toe flexor MAS scores compared to baseline scores ($p>0.05$). FAC and 10-mwt but showed no statistically significant difference at weeks 2 and 12 ($p>0.05$) (Table 3).

Discussion

This study researched the effect of BTX-A injection on spasticity and motor improvement in patients with stroke. It was effective in the shoulder adductor, elbow flexor, wrist flexor and finger flexor, knee extensor and toe flexor muscles MAS at week 2, and shoulder adductor muscle MAS at week 12. Brunnstrom motor recovery stages showed significant improvement in the upper extremity and hand at week 2 and in the lower extremity at week 12.

The severity of hand paresis in patients with stroke has been shown to be associated with spasticity-related disability [15]. Therefore, the reduction of disability should be one of the goals in the treatment of spasticity. Numerous studies have shown BTX-A injections to be an efficient technique of management for spasticity when compared to a placebo. In addition, it has been shown that BTX-A injection is well tolerated [16]. Lim et al. conducted a study with stroke patients in subacute (4 weeks-6 months) and chronic (more than five years) stages of the disease. They observed improvement in the wrist and elbow flexors muscles MAS scores four weeks after BTX-A injection only in patients in the subacute stage. They did not find any significant difference in Brunnstrom recovery stages in either group [11]. Our study found a statistically significant improvement in upper limb spasticity and Brunnstrom recovery stages for the upper limb and hand two weeks after BTX-A injection. However, improvement in the MAS scores continued only for shoulder adduction at 12 weeks post-injection. Although the patients with stroke in this research had a long disease duration, they benefited from BTX-A injections, which decreased spasticity and motor recovery in the upper limb, albeit transiently.

Büyükavcı et al. found a significant decrease in the upper limbs including in the elbow, wrist, and finger flexors muscles MAS at 4 and 12 weeks after BTX-A injection. They also showed that Brunnstrom's recovery stages for the hand increased from 2 to 3 at weeks 4 and 12 [17]. Their study, unlike ours, included patients with a stroke duration of 3-12 months. Takekawa et al. prescribed home-based training after BTX-A injection and assessed the patients only at week 4. They found improvement in upper limb MAS scores and motor functions [18].

Brunnstrom recovery stages in stroke patients depend on the synergy, voluntary movements, and degree of spasticity. According to this staging, stroke patients are initially flaccid and then develop synergistic movements with the onset of spasticity. Later on, as spasticity begins to decrease, isolated motor movements appear. Naghdi et al. found a high correlation between Brunnstrom recovery stages and MAS [8]. Our study found that reducing spasticity with BTX-A injection also improved motor recovery.

Stroke patients have increased levels of dependence caused by difficulty in ambulation. The ability to stand, maintain balance, transition from sitting to standing, and walk require balance and coordination of both lower limbs [19]. As a result, spasticity and paresis in the lower extremities cause difficulty ambulating and an increased risk of falls. Thus, a fundamental goal of rehabilitation in stroke patients should be to reduce spasticity and improve function in the lower limbs.

A meta-analysis by Wu et al. showed a significant reduction in lower limb spasticity in patients with stroke at weeks 4 and 12 after BTX-A injection compared to placebo. It was reported that patients who received BTX-A therapy increased their Fugl-Meyer scores, but there was no significant difference in their gait speed. The study concluded that BTX-A was beneficial and well-tolerated in treating lower limb spasticity after stroke [20]. Our study demonstrated a significant improvement in the knee extensors and toe flexors muscles MAS at two weeks and a statistically significant improvement in Brunnstrom recovery stages in the lower limbs three months after BTX-A injection. However, BTX-A injection did not significantly change in 10-mwt and FAC results.

Oh et al. blindly administered 200 IU BTX-A injection-into the gastrocnemius muscle in stroke patients with ankle plantar flexor spasticity. They grouped the patients according to the stroke duration: first six months, 6-12 months, and 1-2 years. Eight weeks after BTX-A injection, they found a significant improvement in MAS and FAC results in all three groups and a significant improvement in 10-mwt scores in the groups with a stroke duration of fewers than six months and between 6 months and one year [21]. Our study, however, found no statistically signif-

Table 1. General characteristics of stroke patients (n=25).

Age (mean ± SD) (min-max)	54.96±12.84 (26-70)
Gender (n) (%)	
Female	8 (32)
Male	17 (68)
Time since stroke (months) (mean ± SD) (min-max)	31.68±21.86 (4-84)
Type of stroke (n) (%)	
Infarct	14 (56)
Hemorrhage	11 (44)
Hemiplegic side (n) (%)	
Right	11 (44)
Left	14 (56)
Spasticity medication n (%)	
Baclofen	5 (20)
Tizanidine	6 (24)

Table 2. BTX-A injected muscles and BTX-A doses in the upper extremity and lower extremity groups.

Upper extremity group (n=18)	BTX-A doses (IU)	
	mean ± SD	min-max
Pectoralis major muscle	40±0	40-40
Biceps brachii/brachialis muscle	46.54±18.41	25-100
Brachioradialis muscle	40±14.14	30-50
Pronotor teres muscle	44±5.48	40-50
Flexor carpi radialis muscle	40.56±10.74	30-60
Flexor carpi ulnaris muscle	33.33±8.16	20-40
Flexor digitorum superficialis muscle	60.42±18.4	30-100
Flexor digitorum profundus muscle	65±7.07	60-70
Lower extremity group (n=23)	mean ± SD	min-max
Rectus femoris/vastus intermedius muscle	48±10.33	40-40
Gastronemius muscle	92.73±10.32	25-100
Soleus muscle	50±6.32	30-50
Tibialis posterior muscle	52.31±12.35	40-50
Flexor digitorum longus muscle	30±0	30-60
Flexor hallucis longus muscle	21.67±4.08	20-40

Table 3. MAS and Brunnstrom revovery stages before the injection and 2 weeks and 12 weeks after the injection.

	Before the injection	2 weeks after the injection	12 weeks after the injection	Before the injection-2 weeks after	Before the injection-12 weeks after
	(mean ± SD) (median)	(mean ± SD) (median)	(mean ± SD) (median)	p	p
Upper extremity group (n=18)					
Upper extremity BRS	2.67±1.19 (2)	3.06±1.21 (3)	2.78±1.22 (3)	**0.008***	**0.317**
Hand BRS	2±1.53 (1)	2.22±1.56 (2)	2±1.37 (2)	**0.046***	**1.000**
Shoulder adductors MAS	2.24±1.35 (3)	1.47±1.23 (1)	1.65±1.22 (1)	**0.006***	**0.008***
Elbow flexors MAS	2.67±1.14 (3)	1.72±1.18 (1)	2.59±1 (3)	**0.003***	**0.579**
Wrist flexors MAS	3.06±1.83 (3)	2.17±1.58 (2)	2.56±1.42 (2.5)	**0.008***	**0.102**
Finger flexors MAS	2.5±1.25 (3)	1.47±1.33 (1)	2.53±1.33 (3)	**0.002***	**0.715**
Lower extremity group (n=23)					
Lower extremity BRS	3.39±0.84 (3)	3.64±1.18 (3)	3.61±0.94 (4)	**0.096**	**0.025***
Knee extensors MAS	1.87±1.29 (2)	1.3±1.15 (1)	1.78±1.09 (1)	**0.015***	**0.614**
Ankle plantarflexors MAS	3.78±0.52 (4)	3.66±0.65 (4)	3.78±0.6 (4)	**0.083**	**1.000**
Toe flexors MAS	0.7±0.7 (1)	0.47±0.51 (0)	0.7±0.73 (1)	**0.025***	**0.739**
FAC	4.09±0.9 (4)	4.17±0.94 (4)	4.22±0.85 (4)	**0.317**	**0.083**
10-mwt (seconds)	30.99±22.06 (21.1)	28.98±23.14 (21.3)	33.06±25.87 (23.6)	**0.089**	**0.236**

10-mwt: 10 meter walking test, BRS: Brunnstrom recovery stages FAC: Functional Ambulation Categories, MAS: Modified Ashworth scale. *p<0.05.

icant decrease in ankle plantar flexor spasticity, FAC, and 10-mwt results. We injected 70-100IU of BTX-A into the gastrocnemius muscle and 30-60 IU into the soleus muscle. Failure to achieve any reduction in ankle plantar flexor spasticity in our study may be due to lower BTX-A doses and longer stroke durations among patients.

A study investigating the efficacy of high-dose BTX-A injections reviewed eight studies that used a minimum of 600 U on botulinum toxin A or incobotulinumtoxin A and a minimum of 1800 U abobotulinumtoxin A injection. It was shown that higher doses of BTX-A injections effectively improved the spasticity of the upper and lower limbs in patients with stroke. Also, adverse effects are reported to be mild [22].

A meta-analysis by Varvarousis et al. reported that BTX-A injections used in patients with post-stroke hemiplegia decreased MAS scores for the lower limbs and improved 10-mwt results [23]. A meta-analysis by Sun et al. reported that BTX-A injection was effective spasticity, but it could be affected by stroke duration, age of patients, and rehabilitation [19]. Patients in our study may have benefited less from BTX-A injection due to longer stroke durations and a wider range of ages.

BTX-A injection's effectiveness often lasts for 3-4 months

[24]. Therefore, we evaluated patients 12 weeks after BTX-A injections. The reduction in shoulder adductor spasticity continued and there was significant improvement in the lower extremity Brunnstrom motor recovery stage at the 12th week. Demiryurek et al. evaluated both the upper and lower extremities and found a significant improvement in MAS in the elbow, wrist and fingers, leg, knee and ankle at one month and three months [14]. In some of the studies in the literature, patients were evaluated for less than 12 weeks; in others, they were followed up to 12 weeks. However, studies investigating the effectiveness of repeated injections with longer follow-up periods may be more beneficial in terms of investigating the effectiveness of BTX-A on motor recovery.

The strengths of our study are that we evaluated both the upper and lower extremities and that we injected BTX-A under ultrasound guidance, not blindly.

The present study has some limitations: It was conducted with a small number of patients and included a heterogeneous group in terms of severity of hemiparesis, age, and stroke duration. Also, the absence of a control group is another limitation.

Conclusion

In conclusion, BTX-A injection used in stroke patients positively affected upper and lower limb spasticity and Brunnstrom recovery stages. We believe using BTX-A injections as part of rehabilitation would be effective in stroke patients.

Ethical approval

The study was approved by the Health Sciences University Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee (FSM EAH - KAEK 2019/19).

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