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The Evaluation of Botulinum Toxin Injection Effect for Poststroke Spasticity Treatment

İnme Sonrası Spastisite Tedavisinde Botulinum Toksin Enjeksiyonu Etkinliğinin Değerlendirilmesi

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Abstract

Objective: In this study we aimed to evaluate the effectivity of treatment with the botulinum toxin-type A (BTX-A) on spasticity, spasticity-related pain, and the daily living activities in post-stroke patients with upper or lower limb spasticity.

Materials and Methods: A total of 35 (23 right side, 12 left side) post-stroke patients who had upper and/or lower limb spasticity were enrolled to the study. BTX-A (249±41 U) was applied to their affected extremities. The degree of spasticity in the upper (elbow, wrists, and fingers) and lower (leg, knee and ankle) extremities was evaluated before treatment, 1 month, and 3 months after treatment using Modified Ashworth Scale (MAS). Daily life activities and severity of spasticity-related pain were also evaluated using the Barthel index and Visual Analogue Scale (VAS) at the same time points.

Results: The average age of the patients in the study was 60±6 years. Both upper and lower extremities were affected in 69%, whereas upper or lower extremities were affected in 31% of patients. BTX-A provided improvement in severity of the spasticity, pain scale, functionality, and quality of life according to the MAS, VAS, and Barthel indexes.The benefits were sustained in the first 3 months of the post-treatment.

Conclusion: BTX-A in the treatment of post-stroke spasticity is a reliable method in terms of adverse effects, pain reduction, its ability to provide long-term effectiveness, and increase functionality and quality of life.

Keywords: Stroke, spasticity, botulinum toxin, pain

Öz

Amaç: Bu çalışmada, inme sonrası üst ya da alt ekstremite spastisitesi gelişen hastaların tedavisinde Botulinum toksin-tip A (BTX-A) enjeksiyonunun spastisite ve spastisiteye bağlı ağrı tedavisindeki etkinliği ile günlük yaşam aktivitelerine olan etkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmaya inme sonrası üst ekstremite ya da alt ekstremitede spastisite nedenli 249±41 U BTX-A uygulanmış 35 (23 sağ taraf, 12 sol taraf) hasta alındı. Üst ekstremitede dirsek, el bileği ve parmaklarda, alt ekstremitede ise bacak, diz ve ayak bileğinde spastisite derecesi; BTX-A enjeksiyonu öncesi, işlem sonrası 1. ay ve işlem sonrası 3. ay Modifiye Ashworth Skalası (MAS) ile değerlendirildi. Ayrıca BTX-A işlemi öncesi, işlem sonrası 1. ay ve işlem sonrası 3. ay günlük yaşam aktiviteleri Barthel indeksi ile, spastisiteye bağlı ağrı ise Vizüel Analog Skalası (VAS) ile değerlendirildi.

Bulgular: Çalışmaya alınan hastaların yaş ortalaması 60±6 idi. Hastaların %69'unda üst ve alt ekstremite, %31'inde ise üst ya da alt ekstremite etkilenmişti. MAS, VAS ve Barthel indeksi kullanılarak BTX-A'nın tedavi öncesine göre anlamlı olarak spastisite ve ağrı şiddetinde azalma, fonksiyonellikte ve yaşam kalitesinde ise artma sağladığı sonucuna varıldı. Birinci ayda sağlanan faydanın 3. ay takiplerinde de sürdüğü saptandı.

Sonuç: İnmeye bağlı spastisite tedavisinde BTX-A uygulanması yan etki açısından güvenli, hastaların ağrısını azaltan, fonksiyonelliği ve yaşam kalitesini artıran, uzun süreli etkinlik sağlayabilen bir yöntemdir.

Anahtar Kelimeler: İnme, spastisite, botulinum toksin, ağrı

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Introduction

Spasticity due to upper motor neuron disorders was described by Lance in 1980. It is described as increased resistance in muscle tonus or tonic stretch reflexes (speed dependent) accompanied by an increase in muscle stiffness, decrease in muscle width, and increased deep tendon reflexes (1). Spasticity can be in three forms: focal, multifocal, and generalized. Treatment is multidisciplinary including the elimination of triggers, physiotherapy, medical treatment (systemic, regional), and surgery (intrathecal, orthopedic, neurosurgery) (2).

Derived from clostridium botulinum, Botulinum toxin type-A (BTX-A) is a neurotoxin that blocks neuromuscular junctions by inhibiting the release of acetylcholine from presynaptic autonomic and motor neurons. BTX-A, which causes chemical denervation, is one of the regional treatment options for spasticity (2,3,4). BTX-A was shown to have better efficacy than systemic medical agents in the treatment of focal and multifocal spasticity (1,2,3,4,5,6,7). Injecting BTX-A to muscles that are more affected by spasticity, increases the success of treatment (1,2,8).

In this study,we evaluated the efficacy of BTX-A in spasticity and spasticity-related pain, and the effects of BTX-A on daily life activities in patients with post-stroke upper or lower extremity spasticity.

Materials and Methods

Patient Population

Thirty-five patients who were admitted to the neurology clinic of Sakarya University Training and Research Hospital with post-stroke spasticity and were injected with BTX-A into the upper extremity, lower extremity or both, between June 2015 and May 2016, were included in the study.

Findings of neurologic examination; demographic features; time, side, and etiology of stroke were evaluated through retrospective analysis of medical records. The Modified Ashworth Scale (MAS) (a measurement of the degree of spasticity) scores of the patients who had injections into the elbow, wrist, and fingers (upper extremities), and leg, knee, and ankle (lower extremities) were evaluated before the injection and 1 and 3 months after the injection. The Barthel index (functional status after stroke) and visual analogue scale (VAS) (a scale used for measuring the severity of spasticity-related pain) scores were evaluated before the injection and at 1 and 3 months after the injection. Participants who gave informed consent, who were not unconsciousness, who completed the neurologic improvement period (stroke at least 6 months ago), and who had 2 or more MAS scores were included in the study. Patients who were unconsciousness or who had cognitive, linguistic or communicative problems, whose medical records were missing, who had undergone previous BTX-A injections for spasticity or received another treatment for spasticity were excluded. Physiotherapy programs were arranged by physical medicine and rehabilitation specialists for all patients who received BTX-A. This study was approved by the Ethics Commitee of Sakarya University (protocol number: 71522473/050.01.04/69).

Application of Botulinum toxin: Intramuscular injections of 170-350 U BTX-A (Botox®) were given to the patients. Each flacon of BTX-A containing 100 U was diluted with 2 ml of saline. It was injected just after the dilution without waiting. The selection of muscles for injections was made by the same researcher in all patients. The same researcher administered injections to the patients under the guidance of electromyographic monitoring. After the injections, all patients were watched for 30 minutes. No complications were reported.

MAS: MAS is used to measure the severity of spasticity. It is based on the subjective evaluation of resistance that the physician sensed during examination (9).

Barthel index: This is used to evaluate daily life activities after stroke. Status of feeding, washing, self-care, dressing and undressing, bowel and bladder care, toilet use, wheelchair to bed transfer, wheelchair use, walking on smooth surfaces and going up and down stairs are scored. A maximum 100 points can be achieved. Patients with 0-20 points are considered as fully dependent, 21-61 points as highly dependent, 62-90 points moderately dependent, 91-99 points as mildly dependent, and 100 points as fully independent (10).

VAS: Patients are asked to identify the severity of pain on a scale of 0 to 10. The validity and safety of this scale is high (11).

Statistical Analyses

SPSS 16.0 was used for the statistical analyses of the data. Numeric data are given as average values, standard deviations, numbers and percentages. Normality tests of the continous variables were evaluated using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare the numeric data that did not have normal distribution. "Repeated measures analysis of variance" was used to compare the repeated measures of the numeric data. A p value of <0.05 was considered significant for all statistical evaluations.

Results

Thirty-five patients with stroke (20 men, 15 women) were included in the study. The mean age of the patients was 60±6 years (range, 46-71 years). Most (71%) patients had ischemic stroke, and 29% had hemorrhagic stroke. The mean duration passed from the beginning of stroke was 3±1.5 years (range, 1-6 years). In 66% (n=23) of patients, the right side of the body was affected, and the left side of the body was affected in 34% (n=12). In most patients, both lower and upper extremities were affected; only upper extremity 14%, only lower extremity 17%, both were affected in 69%. The amount of BTX-A injected into the patients was 240±41 IU.

There was a significant decrease in MAS and VAS scores and a significant increase in the Barthel index in patients between the prior to injection scores and 1 and 3 months after the injections ($p<0.001$, $p<0.001$, and $p<0.001$, respectively) (Table 1).

Changes in MAS scores are shown in the Figure 1.

According to the VAS scores before treatment, five patients (14.3%) reported no pain, 16 (45.7%) had moderate pain, and 14 (40%) had severe pain. According to the VAS scores at 1 month after the injection, five patients (14.3%) reported no pain, 28 (80%) had mild pain, and two (5.7%) had moderate pain. According to the VAS scores at 3 months after the injection, five patients (14.3%) reported no pain, 25 (71.4%) had mild pain, and five (14.3%) had moderate pain. The mean VAS scores of the patients

1 month after the injection were reduced by 59.5% compared with pre-injection scores. When the 3-month post injection VAS scores were compared with 1 month, VAS scores did not change in 25 patients, whereas they increased by 56.6% in ten patients.

According to the Barthel index scores before treatment, two (5.7%) patients were fully dependent, 24 (68.6%) were highly dependent, eight (22.9%) were moderately dependent, and 1 (2.9%) was mildly dependent. According to the Barthel index scores at 1 month after the treatment; three (8.6%) patients were fully dependent, 16 (45.7%) were highly dependent, 15 (22.9%) were moderately dependent, and one (2.9%) was mildly dependent. According to the Barthel index scores 3 months after the injection, two (5.7%) patients were fully dependent, 18 (51.4%) were highly dependent, 14 (40%) were moderately dependent, and one (2.9%) was mildly dependent. Barthel index scores did not change in 11 patients, but were increased by 35% in 24 patients 1 month after the injection compared with pre-injection scores.

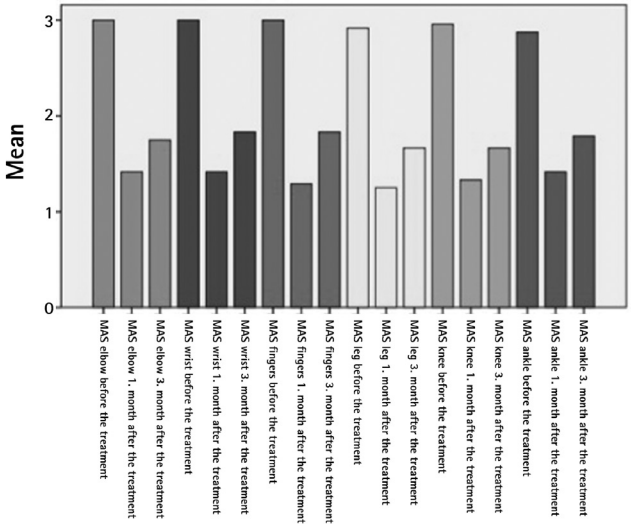

Figure 1. Changes in the Modified Ashworth Scale of extremities of the patients who were performed botulinum toxin, before the treatment, 1. and 3. month after the treatment
MAS: Modified Ashworth Scale

Barthel index scores were significantly better increased at 1 and 3 months after the injection in patients with right-sided stroke compared with patients with left-sided stroke (p=0.03 and p=0.02) (Table 2).

MAS, VAS and Barthel index scores did not differ between patients with ischemic stroke and hemorrhagic stroke (p>0.1, p>0.1 and p>0.1, respectively) (Table 3).

Discussion

In this study, we evaluated the efficacy of BTX-A in the treatment of post-stroke spasticity using MAS, VAS, and the Barthel index, and found that BTX-A improved the severity of spasticity, the severity of pain, functionality, and the quality of life. The improvement achieved 1 month after the injection was maintained 3 months after the injection.

Spasticity is one of the most common and important complications of stroke in the chronic period with a frequency up to 20-40% (12,13,14). The first studies of the application of BTX-A in the treatment of stroke were published in 1989 by Das and Park (15,16). Although oral medications including baclofen, dantrolen, tizanidine, and diazepam have some effects on spasticity, BTX-A has proven to be more effective. Besides better efficacy, BTX-A does not causesystemic adverse events including general weakness of muscles, dizziness, confusion, sedation, nausea, vomiting and diarrhea, which are related with oral medications (6,15). Two types of BTX-A are used in Turkey (Botulinum toxin® and Dysport®). There is no difference between Botulinum toxin and Dysport in terms of efficacy. We used Botulinum toxin in this study. All patients tolerated it well and no local or systemic adverse events were reported.

BTX-A has been used in post-stroke spasticity in many studies, in which BTX-A was injected into lower extremities, upper extremities or both. In some randomized and controlled studies, BTX-A was injected into upper extremities and improvement was achieved in functionality and spasticity but not in pain compared with placebo (16,17,18). Studies in which BTX-A was injected into lower extremities, a significant improvement was achieved in spasticity. There are a few randomized and controlled studies in which BTX-A was injected into both lower and upper extremities (8). Kaji et al. (19) published two randomized and controlled studies in 2010, in which BTX-A was injected into both upper

Table 1. Changes in Modified Ashworth Scale, Visual Analogue Scale, and Barthel index scores in patients with stroke due to application of Botulinum toxin-type A

	Before treatment	1st month	3rd month	p	3rd month-before treatment	1st month- before treatment	3rd month-1st month
MAS-elbow	2.97±0.18	1.41±0.56	1.69±0.66	<0.001	<0.001	<0.001	0.009
MAS-wrist	2.97±0.18	1.41±0.50	1.76±0.68	<0.001	<0.001	<0.001	0.001
MAS-fingers	2.97±0.18	1.38±0.56	1.83±0.65	<0.001	<0.001	<0.001	<0.001
MAS-leg	2.83±0.37	1.33±0.66	1.77±0.67	<0.001	<0.001	<0.001	<0.001
MAS-knee	2.87±0.34	1.47±0.73	1.73±0.69	<0.001	<0.001	<0.001	0.030
MAS-ankle	2.87±0.34	1.47±0.57	1.87±0.62	<0.001	<0.001	<0.001	<0.001
Barthel	49.43±21.65	58.14±20.00	57.86±19.10	<0.001	<0.001	<0.001	0.600
VAS	5.46±2.61	2.17±1.12	2.49±1.22	<0.001	<0.001	<0.001	0.002

MAS: Modified Ashworth Scale, VAS: Visual Analogue Scale

and lower extremities. Spasticity of upper extremity was evaluated with MAS and as a result, after 6 weeks, higher dose BTX-A resulted in lower MAS scores. Spasticity of lower extremities was improved but there was no difference in walking compared with placebo (18,19). In a multi-center, double-blind, randomized, prospective study, the efficacy of BTX-A injection into both lower and upper extremities in patients with stroke was evaluated (20). In this study resulted that BTX-A regards clinical and cost-effectiveness of Botulinum toxin + standard care vs standard care alone in patients with upper and lower limb post-stroke spasticity typically seen in clinical practice. We performed BTX-A injections into the lower and upper extremities of the hemiparetic side in our patients with stroke.

MAS is the most commonly used scale in clinical practice to measure the severity of spasticity. The resistance against passive joint movements is ranked between 0-4 by the physician (21). It was used in most studies in the literature (22,23,24). We used

Table 2. Comparison of clinical features of the patients due to affected body parts and Modified Ashworth Scale, Visual Analogue Scale, and Barthel index scores

	Right (n=23)	Left (n=12)	p
Age	59.7±7	61.1±7.1	0.48
Time of stroke	2.5±1.3	3.8±1.3	0.006
Dose of BTX-A	233±38	281.7±29	0.001
MAS-upper extremity-before treatment	8.8±0.7	9±0	0.81
MAS-upper extremity- 1st month	4.6±1.5	3.7±1.2	0.12
MAS-upper extremity- 3rd month	5.4±3	5.1±1.4	0.85
MAS-upper extremity-Δ month 0-1st month	4.2±1.4	5.3±1.2	0.59
MAS-lower extremity-before treatment	8.6±1	8.5±1	0.55
MAS-lower extremity- 1st month	4.7±1.5	3.6±1.6	0.07
MAS-lower extremity- 3rd month	5.7±1.6	4.9±1.3	0.23
MAS-lower extremity-Δ month 0-1st month	3.8±1.9	4.9±1.5	0.18
Barthel-before the treatment	54.6±24.2	39.6±10.8	0.13
Barthel-1st month	63.1±20.3	48.8±16.4	0.03
Barthel-3rd month	62.8±19.9	48.3±13.7	0.02
Barthel-Δ 1st month-month 0	8.5±9.4	9.1±17.9	0.32
VAS-before the treatment	5.2±3.1	6±1.2	0.91
VAS-1st month	2±1.2	2.4±0.9	0.55
VAS-3rd month	2.4±1.4	2.8±0.8	0.64
VAS- Δ month 0-1st month	3.1±2.1	3.5±1.0	0.82

BTX-A: Botulinum toxin-type A, MAS: Modified Ashworth Scale, VAS: Visual Analogue Scale

Table 3. Comparison of clinical features of the patients with stroke due to etiology, and Modified Ashworth Scale, Visual Analogue Scale, and Barthel index scores

	Thromboembolic (n=25)	Hemorrhagic (n=10)	p
Age (years)	60.4±7	59.8±7.1	0.98
Time of stroke	2.6±1.4	3.6±1.3	0.07
Dosage of BTX-A	238.4±40.8	278±30.5	0.02
MAS-upper extremity-before treatment	8.8±0.7	9±0	0.84
MAS-upper extremity-1st month	4.4±1.5	3.8±1.3	0.35
MAS-upper extremity-3rd month	5.3±2	5.3±1.4	0.77
MAS-upper extremity-Δmonth 0-1st month	4.4±1.4	5.2±1.3	0.22
MAS-lower extremity-before treatment	8.7±0.9	8.4±1	0.35
MAS-lower extremity-1st month	4.7±1.5	3.5±1.7	0.08
MAS-lower extremity-3rd month	5.6±1.6	5±1.4	0.42
MAS-lower extremity-Δ month 0-1st month	4.0±1.8	4.9±1.6	0.30
Barthel-before treatment	52.8±24	41±11.3	0.36
Barthel-1st month	61.2±20.5	50.5±17.4	0.14
Barthel-3rd month	61±20.1	50±14.3	0.11
Barthel-Δ1st month-month 0	8.4±9.1	9.5±19.8	0.28
VAS-before treatment	5.2±3	6.1±1.2	0.73
VAS-1st month	2.2±1.3	2.2±0.8	0.82
VAS-3rd month	2.4±1.4	2.6±0.7	0.87
VAS- Δ month 0-1st month	3.0±2.0	3.9±0.7	0.35

BTX-A: Botulinum toxin-type A, MAS: Modified Ashworth Scale, VAS: Visual Analogue Scale

MAS to measure spasticity in this study and found a statistically significant decrease in MAS scores at 1 and 3 months after BTX-A injection ($p<0.001$).

Spasticity in the weak lower extremity has beneficial effects on mobilization and functionality in the early period; however, increased spasticity adversely affects the quality of life. Functionality is impaired and disability is worsened due to increased spasticity (25,26). To evaluate functional improvement and quality of life, we used the Barthel index. We found a significant increase in Barthel index scores at 1 and 3 months after the injection ($p<0.001$). An increase in the Barthel index might be caused by the injection of BTX-A into both lower and upper extremities, which resulted in an increase in mobilization and functionality and decrease in MAS scores.

BTX-A reduces pain by suppressing the release of acetylcholine, substance P, glutamate, and calcitonin-releasing gene peptide. BTX-A is also used as an analgesic in migraine, diabetic neuropathic pain, and complex regional pain syndrome (27,28). Dunne et al. (29) injected BTX-A (200 or 300 U) into the lower extremities of 85 patients and found a significant decrease in spasticity and pain at the end of 12 weeks. In another study, 500 U BTX-A was injected into the pectoralis major muscle of post-stroke patients for the treatment of spastic shoulder pain and the improvement in pain lasted for 6 months (30). We evaluated the severity of pain with VAS in this study. We found a significant decrease in VAS scores at months 1 and 3 compared with the pretreatment scores ($p<0.001$). Unlike some studies in the literature, we found a significant improvement in both pain and functionality, which may be caused by injection of BTX-A into both lower and upper extremities, instead of only one extremity.

Brashear et al. (31) found a decrease in spasticity, an increase in functionality, and a decrease in pain 12 weeks after BTX-A injection in post-stroke patients with spasticity. We found that the effects of BTX-A at 1 month continued through month 3, which was compatible with the literature. Bhakta et al. (32) showed that the effects of BTX-A were sustained 11 months later in patients who were also involved in a regular rehabilitation program. Findings reported in some studies including a decrease in effectiveness at 12 months and differences in functional status may be caused by insufficient dose, patient selection, existence of contractures, and lack of effective and sufficient rehabilitation program (3,7,10).

An effective physical therapy and rehabilitation program in the early period of stroke is necessary for the improvement of spasticity, and studies showed that a combination of BTX-A and physical therapy and rehabilitation program was better than using them separately (32,33,34,35). In our study, all patients were included in a physical therapy and rehabilitation program in the early period of stroke, which might account for the improvement in all scales.

Application of BTX-A in the early period of spasticity was shown to result in better improvement in functionality in some studies (36,37). The mean duration of stroke was 2.9±1.4 years in our study.

Common adverse effects of BTX-A, which is shown to be safe, are local adverse effects including pain at the area of injection, and weakness of surrounding muscles. Also, dysarthria, dysphagia, dysphonia, respiratory failure, and rarely, death, may be seen. Neutralizing antibodies should be considered in patients who are unresponsive to repeated injections of BTX-A in the long term (38). We did not observe adverse effects due to BTX-A in our study.

Study Limitations

The low number of patients and lack of a control group are the limitations of our study. A few studies evaluated the spasticity of lower extremities after BTX-A injection. Our study, which evaluated the effects of injection of BTX-A into both lower and upper extremities on functionality, is valuable for the literature.

Conclusion

As a result, BTX-A treatment in post-stroke patients with spasticity is a safe method that reduces pain, improves functionality and quality of life and has long-lasting effects. Use of BTX-A in the early period with physiotherapy improves the benefits. Patients with stroke should be followed up for the development of spasticity and their functional status should be evaluated with appropriate scales. Randomized and controlled studies with larger patient populations on this field are needed.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Commitee of Sakarya University (protocol number: 71522473/050.01.04/69), Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Bekir Enes Demiryürek, Aslı Aksoy Gündoğdu, Concept: Bekir Enes Demiryürek, Aslı Aksoy Gündoğdu, Design: Bekir Enes Demiryürek, Aslı Aksoy Gündoğdu, Data Collection or Processing: Bekir Enes Demiryürek, Aslı Aksoy Gündoğdu, Analysis or Interpretation: Bekir Enes Demiryürek, Aslı Aksoy Gündoğdu, Literature Search: Bekir Enes Demiryürek, Aslı Aksoy Gündoğdu, Writing: Bekir Enes Demiryürek, Aslı Aksoy Gündoğdu.

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