Original Investigation / Özgün Araştırma

Efficacy of Botulinum Toxin-Type A Injection for Hand Spasticity Associated with Stroke

İnme ile İlişkili Spastik Elde Botulinum Toksin Tip A Enjeksiyonunun Etkinliği

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ABSTRACT

Objective: We aimed to evaluate of effects of Botulinum toxin A (Btx-A) therapy that used for spasticitiy of upper extremity on pain, range of motion (ROM), spasticity level, dexterity and functionality of hand and independence in daily living activities of patients in this study.

Methods: In this study, the medical records of 35 patients with ischemic stroke were examined retrospectively. Demographic and disease characteristics of patients were recorded. The records including total ROMs, pain, spasticity severity, grip strength, functional and dexterity status of hand and level of independence was recorded. The evaluated parameters before injection of patients were compared with the control results of 1.5 and 3 months after injection.

Results: This study illustrated that the effects of Btx-A continued up to 3 months in terms of improvement of pain levels of elbow, wrist and hand, ROM of wrist and gross hand function. Furthermore; there were significant increases in ROMs of elbow and finger, grip strength, functionality of hand and functional independence in daily living activities 1.5 months after injection compared with the assessment before the injection. The values of these parameters 3 months after injection did not regress to the values of initial assessment. However, there was no significant difference.

Conclusion: Btx-A injections help to increase functional use of the upper extremity in daily living activities of patients. To assess the efficacy of Btx-A injections, its impact on daily living activities and quality of life should be evaluated.

Keywords: Botulinum toxin type A, stroke, spasticity, hand function, rehabilitation

ÖZET

Amaç: Bu çalışmada üst ekstremite spasitistesi için kullanılan Botulinum toksin A tedavisinin ağrı, eklem hareket açıklığı (EHA), spastisite düzeyi, elin beceri ve fonksiyonelliği ile hastanın günlük yaşam aktivitelerindeki bağımsızlığı üzerindeki etkisinin değerlendirilmesi amaçlandı.

Yöntemler: Bu çalışmada iskemik inmeli 35 hastanın tıbbi kayıtları retrospektif olarak değerlendirildi. Hastaların demografik ve hastalık özellikleri kaydedildi. Elin total EHA'ları, ağrı düzeyi, spastisite ciddiyeti, kavrama kuvveti, beceri ve fonksiyonel durumu ile bağımsızlık düzeyi değerlendirildi. Hastaların tedavi öncesi değerlendirilen parametreleri, 1.5 ve 3. Ay kontrol sonuçları ile karşılaştırıldı.

Bulgular: Çalışmada Btx-A tedavisinin dirsek, el bileği ve el ağrı düzeylerinde, el bilek EHA'larında ve kaba el fonksiyonlarında iyileşme bakımından etkisinin 3 aya kadar devam ettiği bulundu. Ayrıca, dirsek ve parmak EHA'ları, kavrama kuvveti, elin fonksiyonelliği ve günlük yaşam aktivitelerindeki fonksiyonel bağımsızlıkta enjeksiyon öncesi döneme göre 1.5 ay kontrolünde anlamlı artış saptandı. 3. Ayda bu değerlendirme parametrelerindeki değerler enjeksiyon öncesi değerlere dönmemesine rağmen, istatistiksel bir farklılık yoktu.

Sonuçlar: Botulinum toksin type A enjeksiyonları hastaların günlük yaşam aktivitelerinde üst ekstremitenin fonksiyonel kullanımını artırmaya yardımcı olmaktadır. Botulinum toksin A'nın etkisini ölçmek için günlük yaşam aktiviteleri ve yaşam kalitesi değerlendirilmelidir.

Anahtar sözcükler: Botulinum toksin tip A, inme, spastisite, el fonksiyon, rehabilitasyon

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Introduction

Stroke is a severe neurological disorder that is encountered throughout the world with advancing age (1). The frequency of spasticity in stroke patients is 16-19% during the acute phase of stroke, and 38-49% during the chronic phase. Traditionally, spasticity defined as a motor disorder characterised by velocity dependent increase in tonic stretch reflexes that can lead to spasm, pain, limitation of joint range and contractures. Upper extremity is a region frequently used for daily living activities; therefore, its spasticity in hemiplegic patients affects skills in daily living activities, functionality and independence of patients (3). In particular, spasticity of flexor muscles at distal part of hemiplegic upper extremity plays a key role.

In recent years, a variety of pharmacological and physical therapy models for the treatment of focal spasticity is used (5). These studies have shown the effectiveness of oral anti-spasticity medications, stretch exercises, cryotherapy, electrical stimulation and orthosis. Additionally, botulinum toxin type A (Btx-A) injection is widely used due to lack of systemic side effects and direct effect on selected muscle group (4, 5).

Some studies have reported an improvement in pain status, limitation of joint movements, motor skills and functionality after Btx-A injection. In contrast, other studies have shown that there is no significant impact on functionality of the hand and overall health (6-8).

In this study; we aimed to evaluate the effects of Btx-A therapy for upper extremity spasticity, as upper extremity is the most common location of dynamic spasticity. Moreover, its spasticity may influence necessary skills and functions in daily living activities of patients, including the pain status, range of motion (ROM), spasticity level of hand, wrist and elbow (as elbow affects the functional status of hand) as well as the dexterity/functionality of hand.

Material and Methods

In this study, the medical records of 35 patients with ischemic stroke hospitalized and treated in our hospital between 2008 and 2012 were examined retrospectively. The inclusion criteria included; having suffered a stroke at latest 6 months prior to the study, not used additional medications for spasticity in the past 3 months and no history of Btx-A injection. The patients and relatives were informed about the treatment method before injection and their written consents were received.

Demographic and disease characteristics including age, gender, dominant hand, affected hand, elapsed time after stroke and etiological cause of stroke were investigated. Passive ROMs of elbow, wrist, thumb and 2nd finger were measured with a goniometer (9). Accordingly, ROMs of flexion, extension, pronation and supination of elbow, flexion and extension of wrist, flexion and extension of 2nd finger and thumb metacarpophalangeal joint (MCPJ), as well as abduction and adduction of thumb MCPJ were recorded. Flexion ROMs of elbow, wrist and fingers were added to their extension ROMs and total ROMs were calculated. Same method was used to calculate pronation, supination ROM of elbow and abduction, adduction ROM of thumb, and total ROMs (10).

Level of elbow and wrist pain evaluated on a 0-10 cm visual analogue scale (VAS) and motor functional stage evaluated by Brunnstrom stages of recovery were recorded. These stages were separately recorded between scores of 1-6 for upper extremity and hand. Modified Ashworth Scale (MAS) was used for the assessment of the spasticity and ranged between scores of 0-4 (11). Grip strength was evaluated with Jamar dynamometer in our routine program. The application of the dynamometer was as follows: elbow flexed 90°, forearm in neutral position, wrist in semipronation and patient at sitting position and asked patient to squeeze dynamometer with maximum strength. The measurements were applied to affected and unaffected hand as 3 consecutive times and the mean value was calculated as score.

Nine hole peg test (NHPT) (12), House scale (13) and Frenchay arm test (FAT) (14) were used for the functional evaluation of the hand.

Pick up and put down periods in NHPT were measured with a chronometer, and periods of 20 seconds and over were evaluated as 'loss of dexterity'. According to the House scale, hand dexterity of patients with scores between 0 and 8; 0 indicates "cannot use" whereas a score of 8 suggests "spontaneous use". In the FAT, patients were asked to perform 5 hand skills. Accordingly, patients were awarded 1 point for each completed hand skill test.

Functional status in daily living was assessed with the functional independence measurement (FIM) and was scored between 18 and 126 (15).

According to the distribution and severity of spasticity in upper extremity affected muscles (brachialis, pronator teres, flexor carpi ulnaris, flexor carpi radialis, flexor digitorum superficialis, flexor digitorum profundus, flexor pollicis longus, flexor pollicis brevis, adductor pollicis, opponens pollicis, interosseous muscles) patients were injected by the same practitioner accompanied by a 10-channel electromyogram (EMG) (Medelek Synergy, Oxford, UK) applying electrical stimulation and detecting motor unit potentials.

In total, 300 units of Btx-A was injected at single use. The dose intervals were between 25-100 IU for brachialis, between 25-50 IU for flexor carpi ulnaris and flexor digitorum superficialis, between 20-50 IU for pronotor teres, flexor carpi radialis and flexor digitorum profundus, between 10-20 IU for flexor pollicis longus, flexor pollicis brevis, adductor pollicis and opponens pollicis, and between 5-10 IU for interosseous muscles.

Patients were evaluated 1.5 and 3 months after injection. Repeated measurements were made by using the aforementioned parameters.

Data analyses were conducted using the Statistical Package for the Social Sciences (SPSS Inc., USA) 15.0 for Windows. Descriptive statistics were presented as mean±standard deviation for continuous variables and observation number and (%) for nominal variables using Chi-Square tests. Possible statistically significant differences between repeated measures were evaluated using Wilcoxon signed rank test. The comparisons within this group were adjusted to Type I error by using the Bonferroni correction. Values of $p<0.05$ were considered indicative of statistical significance.

Results

The mean age of 35 patients treated with Btx-A in our clinic was 45.25±18.32 years, of which 15 (42.9%) of them were female, 20 (57.1%) of them were male. Elapsed time after stroke was 20.68±14.46 months. Suspected cause of stroke was noted to be a combination of hypertension and cardiac disease for 18 (51.4%) patients, hypertension, cardiac disease and diabetes mellitus for 15 (42.9%) patients and only diabetes mellitus for 2 (5.7%) patients. A total of 29 patients (82.9%) were right-handed, whereas the right hand was the affected hand in 22 (62.9%) of patients.

Comparisons of assessments at three time points; before injection, 1.5 months after injection and 3 months after injection, in terms of ROMs of elbow, wrist and hand are shown in Table 1.

At 1.5 and 3. months controls; total ROMS of elbow, wrist and 2nd finger MCPJ are increased compared to before injection ($p=0.004$ in flexion/extension of elbow, $p=0.005$ in pronation/supination of elbow, $p=0.001$ in flexion/extension of wrist, $p=0.033$ in flexion/extension of 2nd finger, respectively), improvement of ROMs of wrist continued at 3. months control (between 1.5 and 3. months $p=0.005$, between before injection and 3. months control $p=0.011$).

Comparisons of assessments at three time points; before injection, 1.5 months after injection and 3 months after injection, in terms of pain level of elbow, wrist and Brunnstrom stage of upper extremity and hand are shown in Table 2.

Pain levels of elbow and wrist were significantly reduced after 1.5 and 3 months compared with the assessment before injection ($p=0.006$, $p=0.006$ in elbow, $p=0.002$, $p=0.008$ in wrist, respectively). Brunnstrom stage of hand increased significantly after 1.5 and 3. months compared with the assessment before injection ($p=0.045$, $p=0.039$, respectively). No significant difference in Brunnstrom stages of upper extremity was detected ($p>0.05$).

Comparisons of assessments at three time points; before injection, 1.5 months after injection and 3 months after injection, in terms of spasticity evaluated by MAS at flexor and pronator muscles groups of elbow, flexor muscles group of wrist, 2nd finger and thumb, as well as adductor muscles groups of thumb are presented in Table 3.

Table 1. Comparisons of assessments at three time points; before injection, 1.5 months after injection and 3 months after injection, in terms of ROMs of elbow, wrist and hand.

Total ROMs	T0 mean±SD	T1 mean±SD	T2 mean±SD
Total ROM for flexion/extension of elbow ° (0-135)	122.17±22.45†	132.82±7.35	127.17±11.94
Total ROM for pronation/supination of elbow °(0-180)	167.39±27.66†	178.26±5.76	173.91±10.43
Total ROM for flexion/extension of wrist° (0-150)	122.39±30.25†	150.00±0.00	143.91±14.37*
Total ROM for MCPJ flexion/extension of 2nd finger° (0-135)	124.56±18.14†	134.34±3.12	133.26±4.67
Total ROM for MCPJ flexion/extension of thumb° (0-50)	46.52±6.11	48.69±4.57	47.69±5.61
Total ROM for MCPJ abduction/adduction of thumb° (0-20)	17.04±5.92	19.13±2.88	18.47±3.51

SD: *Standard deviation,* ***MCPJ:*** *Metacarpophalangeal joint,* ***ROM:*** *Range of motion,* ***T0:*** *Before injection,* ***T1:*** *1.5 months control,* ***T2:*** *3. months control.*

†: *Between T0 and T1 statistical difference is significant ($p<0.05$).*

****:*** *Between T0 and T2, between T1 and T2 statistical difference is significant ($p<0.05$).*

Spasticity was significantly reduced 1.5 months after injection in all muscle groups compared with the assessments before injection (p=0.008 at flexor group of elbow, p=0.001 at pronator group of elbow, p=0.001 at flexor group of wrist, p=0.001 at flexor group of finger, p=0.006 at flexor group of thumb and p=0.001 at adductor group of thumb).

Comparisons of assessments at three time points; before injection, 1.5 months after injection and 3 months after injection, in terms of functional status of hand and functionality in daily life are shown in Table 4.

Grip strength evaluating functionality of hand (p=0.013), House scale used for functionality of hand (p=0.018), FAT (p=0.001) and FIM scores evaluating functionality in daily living activities(p=0.035) significantly increased 1.5 months after injection compared with assessment before injection. The increase in House scale continued after 3. months (p=0.035). There was no significant change in NHPT (p>0.05).

Discussion

This study aimed to evaluate the effects of Btx-A therapy applied by the help of EMG on the spasticity at distal part of upper extremity and pain, limitation of ROM, loss of dexterity/function of hand, and functional independence in daily living activities seen secondary to spasticity. This study illustrated that the effects of Btx-A continued up to 3 months in terms improvement of pain levels of elbow, wrist and hand, ROM of wrist and gross hand function evaluated with House scale. Furthermore; there were significant increases in ROMs of elbow and finger, grip strength, functionality of hand and functional independence in daily living activities 1.5 months after injection compared with assessment before injection. The values of these parameters 3 months after injection did not regress to the values of initial assessment. However, there was no significant difference.

Hand is one of the most functional organs of the body. It is the most active part of upper extremity and

Table 2. Comparisons of assessments at three time points; before injection, 1.5 months after injection and 3 months after injection, in terms of pain level of elbow, wrist and Brunnstrom stage of upper extremity and hand.

Parameters	T0 mean±SD	T1 mean±SD	T2 mean±SD
Pain level of elbow (0-10 cm.)	4.30±4.09†	1.28±2.23	0.93±1.65
Pain level of wrist (0-10 cm.)	4.30±4.17†	0.86±1.79	1.06±1.94
Brunnstrom stage (1-6)			
Upper extremity	3.11±1.27	3.83±1.50	3.82±0.93
Hand	1.80±1.07†	3.02±2.80	2.94±0.88

***SD:** Standard deviation, **T0:** Before injection, **T1:** 1.5 months control, **T2:** 3. months control*

***†:** Between T0 and T1, between T0 and T2 statistical difference is significant (p<0.05).*

Tablo 3. Comparisons of assessments at three time points; before injection, 1.5 months after injection and 3 months after injection, in terms of spasticity evaluated by MAS at flexor and pronator muscles groups of elbow, flexor muscles group of wrist, 2nd finger and thumb, as well as adductor muscles groups of thumb.

Muscle groups that evaluated with MAS	T0 mean±SD	T1 mean±SD	T2 mean±SD
Flexor muscles group of elbow	3.26±2.38†	2.22± 1.95	3.12± 2.08
Pronator muscles group of elbow	3.83± 2.37†	2.30± 1.92	3.63± 2.27
Flexor muscles group of wrist	3.52±2.27†	2.00±1.73	3.29±2.94
Flexor muscles group of 2.nd finger	3.09±2.34†	1.74±1.81	2.85±1.83
Flexor muscles group of thumb	2.70±2.29†	1.70±1.87	2.65±1.93
Adductor muscles group of thumb	2.82±2.29†	1.65±1.77	2.66±1.97

***SD:** Standard deviation, **T0:** Before injection, **T1:** 1.5 months control, **T2:** 3. months control, **MAS:** Modified Ashworth scale*

***†:** Between T0 and T1 statistical difference is significant (p<0.05).*

Table 4. Comparisons of assessments at three time points; before injection, 1.5 months after injection and 3 months after injection, in terms of functional status of hand and functionality in daily life.

Parameters	T0 mean±SD, n(%)	T1 mean±SD, n(%)	T2 mean±SD, n(%)
Hand grip strength (pound)	1,20±2,22†	3,84±3,97	2,53±4,75
House Scale (0-8)	0,91±0,74†§	3,17±1,74	2,83±1,48
NHPT (normal dexterity)	0	5 (14,3)	3 (8,6)
FAT (0-5)	1,35±1,07†	2,65±1,33	2,00±1,24
FIM (18-126)	95,47±24,68†	108,78±18,44	105,00±19,43

***SD:** Standard deviation, **T0:** Before injection, **T1:** 1.5 months control, **T2:** 3. months control, **NHPT:** Nine hole peg test, **FAT:** Frenchay arm test, **FIM:** Functional independence measure*

***†:** Between T0 and T1 statistical difference is significant (p<0.05).*

***§:** Between T0 and T2 statistical difference is significant (p<0.05).*

it is in almost constant contact with the environment. Therefore, hand plays an important role on functional independence. Spasticity after stroke, particularly in distal upper extremity, can be painful and severe enough to affect an individual's ability in daily living activities (3). Therefore, main goals of studies in treatment after stroke are reduction of spasticity and restoration of functionality of patients (4).

Studies applying Btx-A injection to patients with hemiplegia have reported an increase in the ROMs of upper extremity and a reduction in pain levels and spasticity evaluated with MAS which have been ongoing between 1-12 months after injection (16-18). Underpinnings of this wide range of time interval may be due to the ROM, pain level and spasticity are studied in patients with different demographic characteristics in each study. Consensus of these studies is that the maximum increase in ROMs and the maximum reduction in pain level are between 1-4 months. In addition, the maximum reduction in spasticity is between 1-1.5 months. In the present study, improvements in ROMs of hand, wrist and elbow continued up to 3 months was shown. Even if there was no significant difference in between the controls of 1.5-3 months and before injection and control of 3 months; these results are consistent with the literature. The lack of significant difference in ROMs of finger and thumb was due to the absence of serious limitation in ROMs of these joints before injection.

Although numerous studies on the application of Btx-A injection for treatment of spasticity in patients with hemiplegia can be found in the literature; the effect of this treatment on functional status of hand and independence in daily living activities has not been addressed until recently. In recent studies, functions of hand have been shown with measurement of grip strength and the use of various skill tests, but the results of these studies are conflicting. The studies of Wang et al. (19), Bakheit et al. (5), Caty et al. (20) and McCrory et al. (8) found that, although there was an increase in muscle strength between 1.5-4 months after injection, there were no significant improvement in functionality of hand evaluated with Rivermead motor assessment scale, box and block test and Purdue Pegboard test. In contrast, the studies of Kaňovský et al (16), Shaw et al.(17), Kaji et al. (7) and Chang et al. (21) have reported that despite the short lasting muscle strength (1-3 months), improvement in functions of hand particularly in simple and gross upper extremity activities continued up to 12 months.

In the present study, a significant increase in grip strength was displayed 1.5 months after injection. Although this increase did not last for 3 months, it did not regress to pre-injection values either. This is in line with the result that spasticity was improved significantly after 1.5 months. On the other hand, it contradicts the results of other functional and skill tests of the hand. This could be due to static hand strength not completely reflecting the hand function of patient. The hand functions were assessed with NHPT, House scale and FAT tests. While there was no significant change in NHPT, significant improvement after 1.5 months compared with the before injection values were observed in the assessment with House scale and FAT tests. Moreover, House scale analysis displayed an improvement in hand function lasting up to 3 months. It can therefore be suggested that NHPT shows fine hand skills in greater detail than FAT. While not being as sensitive as NHPT, FAT assesses the functionality of hand more detailed compared to House scale which determines gross function of hand. These result show that, although partial, the effectiveness of the injection continues.

Studies evaluating the functional status in daily life have reported that Btx-A injections do not contribute to the functional independence of patients in between 2-4.5 months period. (5,8,20). In Chang et al.'s (21) study which is similar to the present study in terms of the follow up period but differs in rating scale, a significant increase in functional independence was found in daily living activities. Using FIM, Childres et al.(22) injected Btx-A into the muscles of elbow, wrist and fingers of 91 patients with haemorrhagic and ischemic stroke (the mean elapsed time is 26 months) and reported no significant difference in functional independence and quality of life of patients in 9.weeks control.

In the present study, using FIM as an evaluation tool, a significant increase in functional independence in daily living activities was detected in patients 1.5 months after Btx-A injection. This result is in line with the study's other findings which suggest increases in ROM of elbow, hand functionality, grip strength and Brunnstrom stages 1.5 months after injection. The increase in ROM of elbow may enhance the ability of activities in locomotion and transfer sub-groups of FIM, as well as the activities in self-care sub-group which is directly related to hand functionality. Sub-groups of FIM need to be assessed separately for more reliable assessment.

Conclusion

Botulinum toxin A applications in focal spasticity provides significant improvement on the ROM, pain and spasticity of upper extremity especially early after injection. Moreover, these help to increase functional use of the upper extremity in daily living activities of patients. The measurement tools that are used to evaluate the functional disability such as measurement of ROM and spasticity are inadequate to demonstrate the effectiviness of Btx-A injections in patients with hemiplegia. To assess the efficacy of Btx-A injections, its impact on daily living activities and quality of life should be evaluated**.** As a secondary result, demonstration of effectiveness of Btx-A injections are inadequate in hemiplegic patients. To assess the efficacy of Btx-A injections on hand function and daily living activities, tests should be used for the evaluation of the disability that formed due to the dynamic spasticity.

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