Efficacy and Safety of Botulinum Toxin Type A (Botox®) in Blepharospasm and Hemifacial Spasm

Blefarospazm ve Hemifasiyal Spazmda Botilinum Toksin Tip A (Botox®)'nın Etkinlik ve Güvenirliği

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ABSTRACT Objective: Botox®, a preparation of botulinum toxin type A, is most widely used for blepharospasm (BPS) and hemifacial spasm (HFS). In this study, we present 82 patients who have been treated with Botox®. **Material and Methods:** This retrospective study included 15 BPS and 67 HFS patients who admitted to our clinic between May 2007 and December 2011. Botox® was diluted by sterile saline to adjust the dose to 5U/0.1 ml before injection. Pretarsal administration was applied. The average dose of Botox® required for an optimal response was 30-35 MU for BPS, 25-30 MU for HFS. **Results:** The therapeutic effect started after 3 to 5 days, and initial repetitive efficacy intervals (REI) [2nd REI, BPS (13,9 months) and HFS (5,8 months)] were longer than the last mean REI [7th REI, BPS (5.9 months) and HFS (3.7 months)], and there were statistically significant differences between BPS and HFS groups ($p<0.05$). The treatment was effective in both BPS and HFS. Adverse effects occurred in 7.29% of the injection series. **Conclusion:** BTX-A is established as an effective and safe agent in the treatment of BPS and HFS. The side effects of BTA-X administration may be reduced with the help of injection material used and the application technique.

Key Words: Botulinum toxins, Type A; hemifacial spasm; blepharospasm

ÖZET Amaç: Blefarospazm (BFS) ve hemifasiyal spazm (HFS) tedavisinde kullanılan Botox®, botilinum toksin tip A'nın yaygın kullanılan bir formudur. Biz bu çalışmada Botox® uygulaması yaptığımız 82 vakanın tedavi sonuçlarını sunduk. **Gereç ve Yöntemler:** Mayıs 2007-Aralık 2011 tarihleri arasında kliniğimizde Botox® uyguladığımız 15 BFS ve 67 HFS olgusu retrospektif olarak incelendi. Botox® enjeksiyon öncesi serum fizyolojik ile 5U/0,1 ml olacak şekilde sulandırıldı. Uygulama pretarsal yapıldı. Ortalama Botox® dozu BFS için 30 MU, HFS için 25 MU olarak hesaplandı. **Bulgular:** Enjeksiyondan sonra etkinin 3-5 gün içinde başladığı ve başlangıçtaki ortalama etki süreleri (OES) [2. OES, BFS (13,9 ay) ve HFS (5,8 ay)] son ortalama etki sürelerinden [7. OES, BFS (5,9 ay) ve HFS (3,7 ay)] daha uzun bulundu ve BFS ile HFS grupları arasında istatistiksel olarak anlamlı bir fark vardı ($p<0,05$). Tedavi, BFS ve HFS için etkindi. Enjeksiyona bağlı yan etki %7,29 olarak hesaplandı. **Sonuç:** BTX-A, BFS ve HFS tedavisinde kullanılan etkin ve güvenli bir ajandır. BTX-A'nın yan etkileri, kullanılan materyal ve uygulanan teknikler ile azaltılabilir.

Anahtar Kelimeler: Botulinum toksinler, A Tipi; hemifasiyal spazm; blefarospazm

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Blepharospasm (BPS) and hemifacial spasm (HFS) are the most common movement disorders of the craniofacial area. BPS is a focal dystonia characterized by involuntary and forced closure of eyelids due to spasmodic contractions of the orbital and periorbital muscles. The clinical evidence usually starts with involuntary blinks and strong dystonic contractions that may develop in the orbicularis oculi muscles leading to a functional loss of vision. These spasms may spread to nasal, corrugator and

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frontal muscles.[1-3] In contrast to BPS, the clinical evidence of HFS contains unilateral, intermittent, synchronized tonic or clonic contractions of muscles innervated by the facial nerve. Contraction begins from the orbicularis oculi muscle and spreads to the forehead and lower facial muscles.[3,4]

Botulinum toxin type A (BTX-A) has been used as a common and efficient therapy in BPS and HFS since 1985.[5,6] The treatment should start with the lowest effective dose and injection intervals should not be less than 3 months in order to prevent resistance.[7] BTX-A is applied to the orbicularis oculi muscle at 3 or 4 sites. Side effects are rare and may include diplopia, mild facial weakness, ptosis and local ecchymoses.[8] It has been reported that Botox® injections lead to less side effects and especially less ptosis when compared to Dysport® injections.[9]

In this study, we aimed to assess the efficacy and safety of Botox® treatment in patients with BPS and HFS.

MATERIAL AND METHODS

This retrospective study included 82 patients (15 BPS and 67 HFS) who admitted to our clinic between May 2007 and December 2011. Before injections, all patients underwent cranial magnetic resonance (MR)-MR angiography for any differential diagnosis which may need therapeutic management other than BTX-A injections. All patients had underwent carbamazepine treatment without any response. BTX-A (Botox®) was diluted by sterile saline to adjust the dose to 5U/0.1 ml (2 ml for Botox®) before injection. An orange colored-fixed tip injector (0.30 mm x 8 mm Micro-Fine) was used, with 50 MU botulinum toxin in 1 milliliter for the injection. Pretarsal administration was applied. Injections were administered into the orbicularis oculi, the frontalis, the zygomaticus major, the zygomaticus minor, the levator labi superioris, the risorius, the orbicularis oris, the mentalis and the platysma muscles. Anti-platelet and anticoagulant drugs were stopped 24-48 hours before treatment. Patients were assessed at each injection visit and their response was rated on a 0-4 point scale (0=no effect; 4=marked improvement).[10] Patients were also evaluated 15 days after the injection. Successive injection times (Repetitive efficacy intervals=REI) were separately analyzed in both BPS and HFS. The recorded parameters included the age of patients, the sites of injection, the duration of response (month), the dose in mouse units (MU) of BTX-A at each site, and complications. The dates of all BTX-A follow-up visits between the first and last injection visits were also recorded.

The local ethics committee approved the study, and the informed consent was obtained from each subject.

STATISTICAL ANALYSIS

Besides descriptive statistics (means, standard deviations, median, min-max), independent samples t-test and Mann Whitney U test were used for inter-group comparisons. Fisher's exact test was used to compare qualitative parameters. A p value < 0.05 was accepted as statistically significant.

RESULTS

Following cranial imaging (cranial MR-MR angiography), BTX-A injections were administered a total of 82 patients (mean age: 56.72 years; range 30-87 years). We found an inoperable corner tumor in 1 patient. Of the patients, 18 (22%) were males (mean age: 58.19; range: 31-86 years), 64 (78%) were females (mean age: 56.33 years; range: 30-87 years). Spasms were located on the right side in 24 HFS patients (7 males, 17 females), and on the left side in 43 patients (6 males, 37 females). BPS and HFS groups were comparable in terms of age and gender distribution ($p = 0.440$; $p = 0.301$). The mean disease durations were similar in BPS [6 years (0.25-20 years)] and HFS [5 years (1-23 years)] groups ($p=0.605$). Doses of BTX-A injections were adjusted to 30-35 MU in BPS and 25-30 MU in HFS (10 MU into the frontalis and platysma muscles; by dividing into several points, 12.5-25 MU into the musculus orbicularis oculi; by dividing into 4-5 points-subcutaneously, 2.5-5 MU into each other muscle). The mean total dose of BTX-A, the initial dose, and the last dose were calculated (minimum 25 MU -maximum 35 MU). In the HFS patients, 15-20 MU BTX-A was injected into the other side of the face in

order to retain facial symmetry for cosmetic reasons. All patients were invited for a control on the 15th day following the injection. Their mean response score after the injection (rating scale) was 3.33 ± 0.72. The effect was more prominent around the eyes. Perioral injections led to complications such as disordered speech and spillage when drinking water. Complications were observed in 7.29% of the cases, such as; 6 (2.58%) periocular ecchymoses after the injection, 2 (0.86%) ptosis, 3 (1.29%) disordered speech due to perioral weakness, 4 (1.72%) difficulty in eye closure, 1 (0.42%) dry eye and 1 (0.42%) ptosis of lower eyelid and epiphora. In general, the adverse effects were mild and transient. Systemic adverse effects did not occur. When repetitive efficacy intervals of BPS and HFS groups were analyzed, 1st REI and 2nd REI were longer than 6th REI and 7th REI, but there were significant differences between BPS and HFS only in the second (p =0.002) and last REI (p = 0.036) (Table 1). During a follow-up period of over 4 years, the effects of BTX-A lasted longer than 3 months in both groups. However, this effect showed fluctuations in the BPS group, but it was more stable in the HFS group (Figure 1).

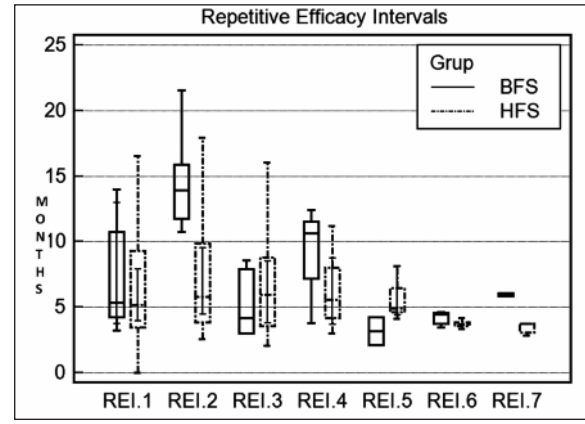

FIGURE 1: Repetitive efficacy intervals in BPS and HFS.
REI: Repetitive Efficacy Interval, BPS: Blepharospasm, HFS: Hemifacial spasm.

DISCUSSION

There are primary and secondary reasons in the etiology of BPS and HFS. The most common cause of HFS is vascular compression of the facial nerve at the root exit zone, most frequently the posterior inferior cerebellar artery. Other sources of compression include tumors in the cerebellopontine angle, arteriovenous malformations and aneurysms.[11] In BPS, secondary BPS is associated with lesions in the basal ganglia, brainstem and thalamus.[12] Disease also may be secondary to Parkinson's disease or neuroleptic drug treatment.[13] For differential diagnosis, cranial MR imaging was performed. The presence of chronic compression leads to nerve demyelination and ephaptic currents which in turn results in paroxysmal pain or spasm.[14] In our group, we found one small ponto-cerebellar angle tumor in only one patient as an etiologic factor, but none of the remaining patients showed any pathology. This was a female patient who complained of involuntary contractions in her face. She was evaluated by a neurosurgeon and diagnosed as inoperable. The patient benefited from BTX-A injections. We failed to find any intracranial pathology in the other cases. Today, BTX-A is the first choice in treatment of BPS and HFS. Jost and Kohl reported 66-98.6% improvement rate, and a mean effect duration of 2-3.5 (months).[15] Various studies reported no difference in efficacy between different BTX-A preparations (Botox®, Dysport®).[9,16,17] However, Nüssgens and Roggenkämper found that Botox® injections led to less side effects and especially less ptosis than Dysport® injections in their comparative study of 212 cases.[9] In our patients, the minimum REI was 3.2 (2.1-4.2) months in BPS, and 3.7 (3.3-4.2) months in HFS (Table 1). Ptosis was observed in 0.86% (n = 2) of the patients as a complication. As BTX-A preparations, Dysport® contains 500 MU (12.5 ng) toxin, whereas Botox® contains 100 units (5ng)

TABLE 1: Repetitive efficacy intervals in BPS and HFS.

REI (month)	BPS (n=15)	HFS (n=67)	p†
1. REI	5.37 (3.23-13.97)	5.165 (0-16.53)	0.397
2. REI	13.9 (10.73-21.57)	5.765 (2.57-17.93)	0.002
3. REI	4.2 (3.03-8.57)	5.935 (2.07-18.27)	0.453
4. REI	10.635 (3.77-12.4)	5.55 (3-15.17)	0.203
5. REI	3.165 (2.1-4.23)	4.9 (4.13-8.13)	0.058
6. REI	4.43 (3.47-4.63)	3.7 (3.33-4.2)	0.297
7. REI	5.95 (5.83-6.07)	3.73 (2.83-3.73)	0.036

REI: Repetitive efficacy interval, BPS: Blepharospasm, HFS: Hemifacial spasm
†Mann Whitney U test.

toxin. In comparison, 1 MU Botox® is almost equal to 3-4 MU Dysport®.[18,19] Dysport® provided a longer benefit duration compared to Botox®; on the other hand, Dysport® caused side effects more frequently. The side effects of BTX-A were mostly characterized by toxin diffusion and local effects. The large size of the 900 kDa complex (Botox®) limits fluid based diffusion of the toxin within the target muscle, whereas lower molecular mass (500 to 700 kDa) of the other preparatoin (Dysport®) causes migration from the injection site.[20,21] In the treatment of BPS and HFS, the most important target is the orbicularis oculi muscle. BTX-A can be injected into different parts of orbicularis oculi muscle (including the orbital, the preseptal and the pretarsal). Cakmur et al. reported that injections into the pretarsal area, the closest part of the orbicularis oculi muscle to the rima, were more successful and caused less ptosis which is the most commonly seen adverse side effect.[22] Side effects are mostly transient, and ptosis, diplopia, blurred vision, dry eyes and ecchymoses on eyelids may last 1-4 weeks. Lagophtalmus and ptosis were more common in Dysport® treatments probably due to its wider diffusion property from the site of the injection. Failure in BTX-A treatment is mainly due to inadequate dosages, flawed injection technique, wrong diagnosis (congenital ptosis or apraxia of eyelid opening), and drug resistance due to antibody formation in cases who received higher doses with frequent intervals. In their study, Kwan et al. reported that the toxin treatment was safe, with a 10% complication rate in 170 patients with HFS.[23] In our study, the complication rate was 7.29% (including ecchymosis of the injected region, ptosis, and lower facial weakness). Ecchymoses was observed in 2.58% (n=6) of the patients. However, these were during the first treatments and there was a positive history of antiaggregant or anticoagulant use. Our later treatments showed lesser complications (due to the fact that we prohibited the use of these drugs 24-48 hours before injections). A female patient showed lower eyelid ptosis and epiphora. In the latter injections, the lower eyelid lateral area was not used, and these complications were prevented. Lower facial weakness was another complication which led to speech and eating disorders. Lower complication rates in our study may be due to the selected method as pretarsal administration etc. and the material (injector, etc.) used. Mejia et al. concluded that by minimizing antibody formation risk, the efficacy of the treatment might continue even after 18 years in BTX-A treated patients.[24] In our study population, the mean disease durations were 6 (3 months-20 years) years in BPS and 5 (1-23) years in HFS. We performed BTX-A treatment over a 4 year-period. Our Botox® efficacy score was 3.33 ± 0.72. Drummond and Hinz found the mean duration of benefits was 15 weeks for HFS patients and 12 weeks for BPS patients.[25] In our study, the mean effect duration was higher in earlier periods and then decreased in later periods. The therapeutic effect started 3-5 days later, and the mean total duration of response initially was longer than last REI in BPS and HFS (Table 1). These results suggested development of drug resistance, nevertheless, the effect duration did not shorten less than 3 months. Most studies have commented on the fact that 95% of patients had some degree of improvement in their condition.[13,26,27] In another study, Cannon et al. found that 90% of patients were satisfied with the effect of their last BTX-A treatment.[28] This satisfaction rate was higher in patients with HFS compared to the patients with BPS.[28] In our study, efficacy seemed to be better in BPS compared to HFS, but it was more stable in HFS after injections, whereas the efficacy trend showed up and down alterations in BPS (Graphic 1). This difference between the groups may be due to the small number of patients in the BPS group.

In conclusion, BTX-A is established as an effective and safe treatment for involuntary facial movements. In our study, BTX-A was effective for both HFS and BPS, but duration of efficacy was longer in BPS. Side effects of BTA-X administrations may be reduced with the help of injection material used and the application technique, as in our study. Since drug resistance due to antibody formation may develop, long-term follow-up is necessary.

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