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Efficacy of botulinum toxin A for treatment of unilateral spasms of the eyelid and its prognosis

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Abstract. – BACKGROUND: To this date, only a small number of studies have described the long-term use of BTX in Hemifacial spasm.

AIM: To assess the prognosis and long-term effectiveness of Botulinum toxin A (BTXA) in the treatment of unilateral spasms of the eyelid.

PATIENTS AND METHODS: From September 1998 to January 2006, 245 consecutive cases of unilateral spasms of the eyelid were included in this retrospective study. Among them, 143 patients (BTXA group) underwent BTXA injection treatment, and 102 patients did not receive any intervention (control group). BTXA injections were made subcutaneously around the eye with the dose of 2.5U other than the temporal canthus of 5U. Follow-up was performed for 1-7 years after the last injection.

RESULTS: In BTXA treatment group, the complete remission rate was 78.3% (112/143), recurrence rate was 21.7% (31/143) and the incidence of hemifacial spasm (HFS) was 18.9% (27/143); complete remission rate for patients with disease duration less than 3 months was 96.6% (86/89); for patients with a 3-6 months disease history, complete remission rate was 75.8% (25/33), and patients having the disease course exceeding 6 months had a complete remission rate of 4.8% (1/21). In the control group, the complete remission rate was 12.7% (13/102), and the prevalence of HFS was 71.6% (73/102); 16.7% (9/56) of patients with the disease duration less than 3 months were remitted, but the complete remission rate was 12.9% (4/31) for patients with a 3-6 months disease history. None was in remission when the disease history exceeded 6 months.

CONCLUSIONS: BTXA treatment can improve the complete remission rate and prevent further progression of unilateral spasms of the eyelid into HFS, especially in early stage.

Key Words:

Efficacy, Botulinum toxin A, Unilateral spasms, Eyelid, Prognosis, Treatment..

Introduction

Hemifacial spasm (HFS), first described by Gowers in 1884, is the most common peripherally induced movement disorder[1]. HFS is characterized by unilateral, intermittent contractions of the muscles of facial expression, which usually originates in the lower eyelid before progressing to involve the upper eyelid and the whole facial muscles in the fourth or fifth decade of life[2,3]. Therefore, unilateral spasms of the eyelid and perioral muscles innervated by the facial nerve may be an early sign of HFS[4].

The anatomical basis for the HFS is believed to be mechanical irritation of the facial nerve at its exit root by compression from one or more adjacent arteries or veins[5,6]. Although it is not a life threatening condition, it may cause significant cosmetic and functional disability[7]. Other than neurosurgical microvascular decompression procedure[8], recent studies show that botulinum toxin A injection may be an effective alternative in controlling HFS[9,10]. Botulinum neurotoxin A (BTXA) was introduced by Elston in 1986 for therapy of HFS[11] which was then approved by the Food and Drug Administration in 1989. Since then, BTXA has replaced eyelid surgery as the first-line therapy for HFS as it is very successful in controlling eyelid spasms[12-14].

Since treatment response is only transient, most patients need repeated injections of BTXA for many years. Thus, it is important to gather information concerning the safety and efficacy of the long-term treatment. However, to this date, only a small number of studies have described the long-term use of BTX in HFS[6,15-17]. Importantly, it remains unknown whether BTX treatment has an effect on the development of unilateral spasms of the eyelid into HFS. Therefore, a retrospective study was performed here to assess

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the prognosis and relative long-term outcome of 143 patients over the past 7 years who suffered unilateral spasms of the eyelid and had ever received BTX in our Hospital.

Patients and Methods

A review of medical records of 245 consecutive patients diagnosed with unilateral spasms of the eyelid at the Out-Patient Department of Otolaryngology, Ophthalmology and Neurology in our Hospital between Sep 1998 and Jan 2006 was done. Among them, 143 patients received local BTXA injection treatment (BTXA group) and 102 patients did not receive any therapeutic intervention (control group). All patients underwent a complete history taking and physical examination to rule out the neurological diseases and other secondary unilateral spasms of the eyelid, such as induced by otitis media mastoiditis, space-occupying lesions of the cerebellopontine angle, sequelae of facial nerve, anaesthesia, encephalitis, arachnoiditis, multiple sclerosis, Paget's disease, and basilar invagination. The bilateral spasms of the eyelid patients were also excluded. Cranial computed tomography (CT) and magnetic resonance imaging (MRI) examinations demonstrated no abnormalities in all the included patients.

BTXA used in this study was supplied by the Lanzhou Institute of Biological Products (Lanzhou, China, [97]-Ministry of Health drug approval no.-[Lan]-S-01). To treat unilateral spasms of the eyelid, BXTA injections were performed subcutaneously 2-3 mm from the lid margin in the inner and outer thirds of the upper or lower eyelid and also subcutaneously 5 mm from the temporal canthus (total 5 sites, Figure 1). The concentration of BTXA used was 25 U/mL, and the dose injected at each site was 2.5 except of 5.0U in the temporal site. The orbicularis oculi was re-injected if there were residual contractions after one week. As a result, 60 patients received once reinjection and 2 patients needed twice reinjection with the similar dose. One of the authors performed all the injections (LS).

The severity of spasm was graded clinically from grade 0 to grade IV according to Jankovic disability rating scale[18] : "0", no abnormality, normal blinking; "I", Increased blinking rate caused by external stimuli; "II", Eyelid 'fluttering' and tending to close, no sustain disfigurement; "III", Noticeable spasm; mildly incapacitating; and "IV", Severe, prolonged disfigurement; incapacitating social activities.

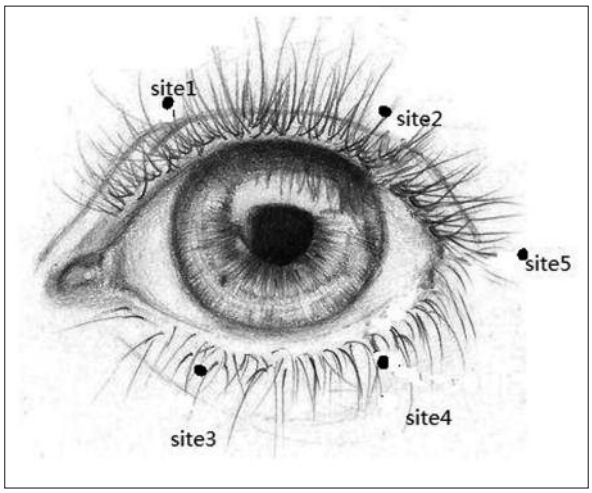

Figure 1. Injection sites of botulinum toxin A in the treatment. Site 1 and site 2: lid margin in the inner and outer thirds of the upper eyelid; site 3 and 4: lid margin in the inner and outer thirds of the lower eyelid; site 5: the temporal canthus.

Complete spasm remission was defined from grade II-IV to grade 0 and this remission could not change for more than 3 years after the last injection. Clinical recurrence was defined as recurrence of spasm symptoms, after the last injection, which persisted for more than 3 weeks. All patients were followed by outpatient appointments, and the follow-up duration ranged from 1 to 7 years.

Statistical Analysis

All the data analyses were performed using SPSS for Windows (version 11.5, SPSS Inc., Chicago, IL, USA). The chi-square test was used to compare the demographic data, remission rate and the incidence of hemifacial spasm difference between two groups. Statistical significance was defined at $p < 0.05$.

Results

Demographic data for patients in each group are shown in Table I. A total of 143 patients (67 male and 76 female) were given local BTXA injection treatment. The mean age of patients was 42 ± 2.8 years (range, 26-61 years). The mean disease duration from the time of diagnosis to the initial treatment was 4.2 ± 1.4 months (range, 3 weeks to 1 year), including 89 cases less than 3

Table I. Demographic data for patients with unilateral spasms of the eyelid treated with botulinum toxin A injections or without.

Group	BTXA (N=143)	Control (N=102)	*p*-value
Sex (N)			
Female	76	63	>0.05
Male	67	39	
Mean age (years)	42 ± 2.8	44 ± 3.4	>0.05
Mean disease duration (months)	4.2 ± 1.4	5.3 ± 1.2	>0.05

months, 33 cases within 3-6 months, and 21 cases over 6 months. Ten patients had grade II spasm, 93 had grade II, and 40 had grade IV spasm. The remaining 102 patients (39 males and 63 females) did not receive any therapeutic intervention. The ages of patients in this group ranged from 35 to 56 years, with a mean age of 44 ± 3.4 years. The mean disease duration was 5.3 ± 1.2 months (range, 4 weeks to 11 year), including 56 cases less than 3 months, 31 cases within 3-6 months, and 15 cases over 6 months. Seven grade II, 78 grade III, and 17 grade IV patients were included in this group. There was no significant difference in each parameter between two groups.

Patients were assessed 4.0 months after the last injection of BTX-A (Table II). In the BTXA treatment group, complete remission was observed in 112 patients (78.3%). In the control group, complete remission was observed in 13 patients (12.7%). Seven-year follow-up results indicated that 31 patients (1.7%) developed recurrences and 27 patients (18.9%) progressed to HFS in the BTXA treatment group. In the control group, 9 patients (8.8%) developed recurrences and 73 patients (71.6%) progressed to HFS (Table II). The chi-square test indicated the complete remission rate was significantly improved in BTXA treatment group and the prevalence of HFS was significantly higher in control group ($p < 0.05$).

Furthermore, we also attempted to correlate disease history and remission rate. In the BTXA treatment group, complete remission rate for patients with disease duration less than 3 months was 96.6% (86/89); for patients with a 3-6 months disease history, complete remission rate was 75.8% (25/33), and patients having the disease course exceeding 6 months had a complete remission rate of 4.8% (1/21). These findings indicated the complete remission rate was significantly higher for those patients with a disease history of less than 3 months (96.6%) compared to those patients with a disease history of more than 3 months ($p < 0.05$). In the control treatment group, 16.7% (9/56) of the patients with the disease duration less than 3 months were in remission, but the complete remission rate was 12.9% (4/31) for the patients with the disease duration between 3 and 6 months. None of patients were in remission when the disease history exceeded 6 months (Table III).

Discussion

Botulinum toxin, an exotoxin produced by C. botulinum, causes a pre-synaptic block at the neuromuscular junction. The toxin enters the presynaptic terminal where it causes proteolysis of the SNARE (soluble N-ethylmaleimide sensitive factor attachment protein receptor) proteins, which are responsible for the docking and fusion of the synaptic vesicles, resulting in failure of acetylcholine release[19,20]. However, the effect of botulinum toxin A is considered temporary and the muscle weakness is reversible. New axonal sprouting occur within a few days, followed by gradual recovery of the poisoned original parent

Table II. The prognosis of BTXA treatment.

Group (N)	Pre-treatment severity (N)	Post-treatment severity (N)	Remission rate	Recurrence rate	Prevalence of HFS
BTXA (143)	Grade II (10) Grade III (93) Grade IV (40)	Grade 0 (112) Grade I (17) Grade III (14)	78.3% (112/143)	21.7% (31/143)	18.9% (27/143)
Control (102)	Grade II (7) Grade III (78) Grade IV (17)	Grade 0 (13) Grade I (13) Grade III (3)	12.7% (13/102)	8.8% (9/102)	71.6% (73/102)

Table III. The relationship between disease course and remission rate.

Group	Disease course	Pre-treatment Severity (N)	Post-treatment Severity (N)	Remission rate
BTXA	< 3 months	Grade II (8) Grade III (75) Grade IV (6)	Grade 0 (86) Grade I (2) Grade II (1)	96.6% (86/89)
	3-6 months	Grade II (2) Grade III (13) Grade IV (18)	Grade 0 (25) Grade I (3) Grade II (5)	75.8% (25/33)
	> 6 months	Grade II (0) Grade III (5) Grade IV (16)	Grade 0 (1) Grade II (6) Grade III (14)	4.8% (1/21)
Control	< 3 months	Grade II (4) Grade III (51) Grade IV (1) Grade III (37) Grade IV (1)	Grade 0 (9) Grade I (1) Grade II (8)	16.7% (9/56)
	3-6 months	Grade II (2) Grade III (23) Grade IV (6) Grade IV (4)	Grade 0 (4) Grade II (6) Grade III (17)	12.9% (4/31)
	> 6 months	Grade II (1) Grade III (4) Grade IV (10)	Grade III (3) Grade IV (12)	0 (0/15)

terminal over the next few months[21]. Patients require regular injections to maintain benefit. Thus, it is important to investigate the relative long-term efficacy of BTXA for treatment of unilateral spasms of the eyelid. In this study, we found in BTXA treatment group, 78.3% of patients (112/143) remained in remission after 3 years, however, only 12.7% of patients were in remission (13/102) in control group, which was significantly less than those remitted in the BTXA treatment group ($p < 0.05$). This result suggested BTXA intervention could significantly improve the complete remission rate. This may be involved in hyperexcitable neurons in the facial nerve neuron that remain in a reversible state, but the mechanism needs further research.

Although many papers have recommended that BTXA injection is an effective method to treat HFS, the prognosis of BTXA treatment whether having an effect on the development of unilateral spasms of the eyelid into HFS is poorly reported so far. In this study, we found most of patients in BTXA treatment group were remitted (112/143), only a small part of patients developed to HFS (27/143). Most of patients in control group developed to HFS (73/102). These results suggested that the unilateral spasms of the eyelid could progress into HFS in both groups, but the incidence in BTXA treatment group was significantly lower than that of the control group. These results seemed to be in accordance with our above conclusion that BTXA significantly improved the remission rate and thus reduced the incidence of HFS progression[22-24].

At least two reasons help us explain why clinical HFS has traditionally been viewed difficult to cure. For one, early symptoms, such as unilateral spasms of the eyelid are subtle in the majority of HFS patients. The symptoms do not attract sufficient attention, which delays the opportunity for early treatment. Additionally, physicians generally do not emphasize early interventional treatment[25-27]. Early intervention is defined as a treatment strategy combining early detection of disease risk and treatment implementation. Treatment can be offered to patients before they request it, or (as is often the case) provided to patients before they realize they have a health problem[28,29]. In this study, we further examined the relationship between spasm disease history and therapeutic efficacy of BTXA. Of the 143 patients in BTXA treatment group, 89 patients had a disease duration of less than 3 months, and 86 of these patients were remitted (96.6%); 33 patients had a disease history between 3 and 6 months, and 25 were remitted (75.8%); 21 pa-

tients had a disease course exceeding 6 months, and 1 was remitted (4.8%). In the control treatment group, 16.7% (9/56) of the patients with the disease duration less than 3 months were remitted, but the remission rate was 12.9% (4/31) for the patients with the disease duration between 3 and 6 months. None was in remission when the disease history exceeded 6 months. Therefore, the remission rate was the highest in patients having the disease course less than 3 months ($p < 0.05$). These findings also suggest that early interventional treatment with BTXA can achieve a satisfactory clinical goal for curing unilateral spasms of the eyelid.

These results indicate, regardless of BTXA treatment or without, the remission rate is the highest in patients having the disease course less than 3 months. This may result from the increased probability in a reversible state of hyperexcitable neurons in the facial nerve neuron. However, the safety and efficacy of BTX is now under controversy.

Currently there are only four BTX products commercially available in the US Food and Drug Administration approved for various therapeutic and cosmetic indications, with an expanding list of off-label therapeutic use[30], so researchers worry about the safety and efficacy about BTX[31]. However, based on their 20-year longitudinal study and published reports with at least 5-year follow-up, Castaneda et al 32 report that BTX is a safe and effective long-term treatment for focal and segment dystonia. Santamato et al[33] study the efficacy and safety of higher doses of BTXA NT 201 (a new BTXA free of complexing proteins, up to 840 U) in 25 consecutive patients with upper and lower limb spasticity after stroke, and indicated that higher doses of BTXA NT 201 appeared to be safe and efficacious. In a prospective observational study determining the safety and the self-reported efficacy of BTX injections for adult spasticity in current clinical practice, BTX is proved to be effective and safety[34]. Thus, BTXA used in this study is safe.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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