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ORIGINAL ARTICLE

A comparative crossover study on the treatment of hemifacial spasm and blepharospasm: preseptal and pretarsal botulinum toxin injection techniques

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Abstract Hemifacial spasm (HFS) and benign essential blepharospasm (BEB) are chronic and disabling abnormal craniofacial movements that produce involuntary eyelid twitching and closure. The efficacy and safety of botulinum toxin type A (BoNT-A) injections have been accepted and widely used for the treatment of HFS and BEB. However, different injection sites may influence the effectiveness, doses, and side effects. The aim of this study is to compare the efficacy, patient satisfaction, and complications of low-dose BoNT-A injections between injection at the preseptal (PS) and the pretarsal (PT) portion of the orbicularis oculi muscle. A total of 40 patients, 31 patients with HFS and 9 patients with BEB, participated in this study. Each patient received both PS and PT BoNT-A injections in a crossover design study. Latency to response, duration of improvement, the Jankovic Rating Scale (JRS), self-response scale, patient satisfaction scale, and complications were compared. Low-dose injections of BoNT-A at the PT portion produced a significantly higher response rate in terms of latency to response, duration of improvement, JRS, self-response scale, and patient satisfaction scale than the PS injections. Major side effects including ptosis and droopy eyelid were observed only after the PS injections. These findings confirmed that low-dose injections of BoNT-A at the PT portion provide more efficacy, patient satisfaction, and fewer complications than the PS injections for the treatment of involuntary eyelid twitching and closure in patients with HFS and BEB.

Keywords Hemifacial spasm · Blepharospasm · Botulinum toxin · Pretarsal · Preseptal

Introduction

Hemifacial spasm (HFS) and benign essential blepharospasm (BEB) are common, chronic, and disabling abnormal craniofacial movements. Patients with HFS usually present with frequent involuntary unilateral eyelid twitching and gradually spread to include the muscles around the mouth and neck on the same side, in contrast to BEB which is associated with involuntary and sustained contractions of the muscles around the eyes. Despite the difference in pathophysiology, both disorders result in uncontrollable contractions of the orbicularis oculi muscle (OOM) causing an impairment of vision, facial expression, and have an impact on quality of life [1–3].

Long-term efficacy and safety of botulinum toxin type A (BoNT-A) injections have been evaluated and widely accepted for the treatment of HFS and BEB [4–8]. However, the injection sites, doses, and techniques are variable. Typically, the total dose of onabotulinumtoxinA (Botox®, Allergan) used for the treatment of HFS and BEB ranges from 10 to 34 (mouse) units and from 25 to 50 units, respectively, with the average treatment interval of 3–4 months [9, 10]. As the treatment requires repeated and long-term injections, patients who receive high-dose injections may be at risk for immunologic reactions with possible formation of neutralizing antibodies and secondary treatment failure [11]. However, treatment failure may be related to underlying disease severity,

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dose, and injection technique [12–15]. Injection into the pretarsal (PT) part of the OOM has been reported to have a better outcome and fewer side effects than that of the preseptal (PS) or orbital part in previously published observational and retrospective studies [13–16]. Here, we prospectively compared the efficacy, safety, and patient satisfaction of a low-dose BoNT-A injection between the PS and the PT areas on the treatment of HFS and BEB in a crossover design study.

Patients and methods

A prospective, randomized, double-blind, crossover design study was conducted between June 2015 and September 2016 at the botulinum toxin clinic, Thammasat University Hospital. Patients included in the study were diagnosed with HFS or BEB by a neurologist with expertise in movement disorders. General demographic data of each patient and pre-treatment Jankovic Rating Scale (JRS) were recorded [17]. The exclusion criteria were a history of allergic reaction to BoNT-A, patients with generalized muscle weakness, patients with clinically suspected eyelid opening apraxia, and facial synkinesis [18, 19].

In the first period of the study, patients were consecutively randomized with a 1:1 ratio into two study arms: the PT injections and the PS injections. Both groups were injected with onabotulinumtoxinA (Botox®, Allergan) with the dilution of 100 units per 2 ml, 2.5 units at each point: two injections at the medial and lateral segments of the upper eyelid and two injections at the middle and lateral segments of the lower eyelid (Fig. 1). The cumulative dose was not more than 10 units per eyelid. All patients were injected subcutaneously with a 30-gauge, 0.5-in. needle with an insulin syringe when lying on an examining bed with eyes closed by the same injector. In the HFS group, additional sites in the orbicularis oris, zygomaticus major, levator labii superioris, and the mentalis muscles on the affected site were also used. The cumulative total dose of onabotulinumtoxinA in our study was around 20 units per patient.

Patients were asked to fill a symptom diary that included latency to response, latency to the peak of efficacy, duration of response, and complications. A telephone interview by a neurologist who was unaware of the treatment groups was assessed at the following month. The patients were advised to score their condition using a 7-step analog scale (−1 = worsening, 0 = no benefit, 1 = minimal or questionable benefit, 2 = mild response, 3 = moderate response, 4 = marked response, 5 = striking improvement) and a 10-numeric satisfaction rating scales (0 = not satisfied and 10 = very satisfied) [20]. Following at least a 3-month washout period, the patients were reinterviewed and assessed by a neurologist who was blind to the patient groups at the clinic. The patients whose JRS returned to the baseline had then received a crossover treatment, while the patients who still gained some benefit from the last injections were delayed in the crossover treatment (Fig. 2). Since the study was aimed to compare the efficacy of the PS and PT injections, assessments in patients with HFS were focused on the response and complications of the orbital area. In patients with BEB, clinical outcomes of each technique were assessed on the average response from both sides of the orbital area. The study protocol was approved by the local Human Research Ethics Committee.

The quantitative data were analyzed by mean with standard deviation. The efficacy, patient satisfaction scale, and other rating scales were compared between groups by Wilcoxon matched-pairs signed-rank test. A p value of less than 0.05 was considered statistically significant.

Results

A total of 40 patients, 31 patients with HFS and 9 patients with BEB, participated in the study. Demographic and clinical features of the study population are shown in Table 1. The total cumulative dose of onabotulinumtoxinA was 18.75 ± 2.39 units (range 12.50–22.50 units) and 9.56 ± 1.11 units per eyelid (range 5–10 units). Both techniques produced a significant improvement of the symptoms by the post-treatment JRS (3.25 ± 0.83 vs 1.38 ± 0.51, $p < 0.001$). The PT injections produced a significantly higher response rate in terms of latency to response (5.85 ± 3.50 vs 8.63 ± 7.33 days, $p = 0.014$), latency to the peak of efficacy (16.38 ± 11.45 vs

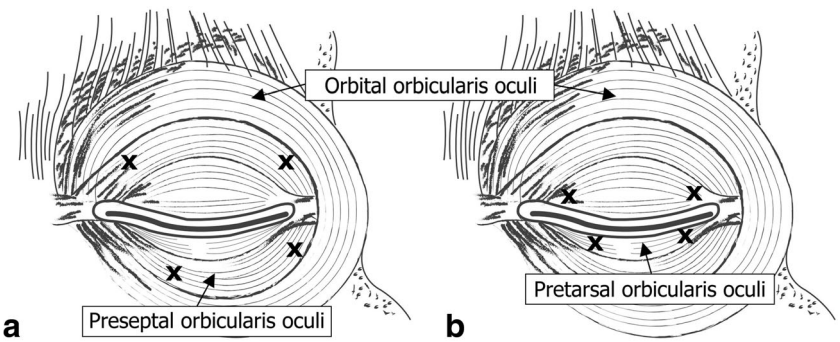

Fig. 1 **a** Preseptal injection sites. **b** Pretarsal injection sites

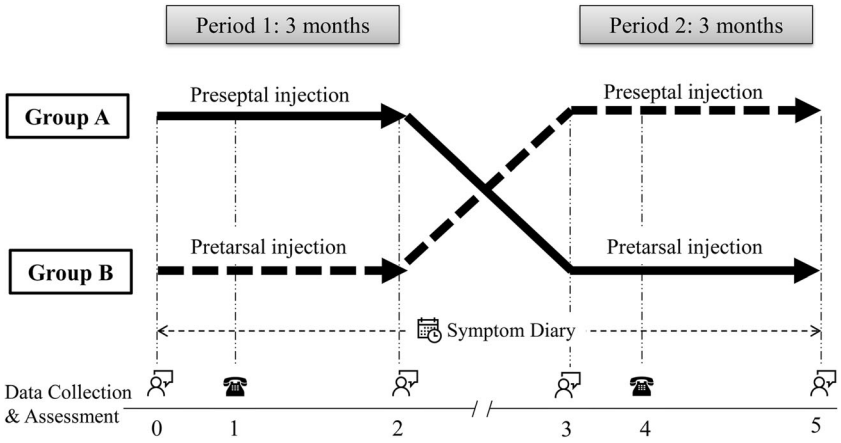

Fig. 2 The study protocol

20.43 ± 13.92 days, $p = 0.019$), duration of response (10.48 ± 1.78 vs 9.63 ± 1.78 weeks, $p = 0.005$), the post-treatment JRS (1.18 ± 0.39 vs 1.58 ± 0.55, $p < 0.001$), self-response scale at 1 month (3.83 ± 0.59 vs 3.48 ± 0.71, $p = 0.018$) and 3 months (3.68 ± 0.62 vs 3.35 ± 0.70, $p = 0.007$), satisfaction rating scale at 1 month (8.28 ± 1.30 vs 7.38 ± 1.64, $p = 0.001$) and 3 months (8.15 ± 1.27 vs 7.20 ± 1.52, $p < 0.001$) than the PS injection technique without a significant difference of the total and cumulative dose per eyelid. The results of both techniques are summarized in Table 2.

When outcomes between HFS and BEB subgroups were compared, the total and cumulative dose per eyelid were not statistically different between the injection techniques. There was a significantly higher response rate for PT injections in both subgroups according to the post-treatment JRS, duration of response, and satisfaction rating scale at 1 and 3 months. Latency to response was found to be shorter with PT injections in both subgroups, but only the BEB subgroup showed a statistically significant difference. Latency to the peak of efficacy and self-response scale at 1 and 3 months were better with PT injections in both subgroups, but statistically significantly significant only in HFS subgroup (Table 2).

Regarding injection complications, minor side effects such as tearing and irritation were found in 6 patients (15%) with the PS injections and 2 patients (5%) with the PT injections. A hematoma developed in 1 patient (2.5%) and 3 patients (7.5%) with the PS and PT injections, respectively. Major side effects such as ptosis or droopy eyelid were found in 3 patients (7.5%) with the PS injections, but none with the PT injections (Table 3). After completing the crossover treatment, approximately two-thirds of the patients preferred the PT injection technique and requested for further treatment with the PT injections.

Table 1 General demographic data of the study population

Demographic data	Hemifacial spasm $n = 31$	Blepharospasm $n = 9$	All patients $n = 40$
Sex			
Female	19 (61.3%)	8 (88.9%)	27 (67.3%)
Male	12 (38.7%)	1 (11.1%)	13 (32.5%)
Symptomatic side			
Right	13	–	13
Left	18	–	18
Bilateral	–	9	9
Age (years)	59.77 ± 9.99	68.00 ± 7.12	61.63 ± 9.97
Duration of disease (years)	5.55 ± 4.95	4.78 ± 5.87	5.38 ± 5.10
Duration of previous treatment with BoNT-A injections (years)	2.19 ± 2.32	1.56 ± 3.28	2.05 ± 2.53
Pre-treatment JRS (1–4)	3.25 ± 0.89	3.22 ± 0.65	3.25 ± 0.83
Post-treatment JRS (1–4)	1.39 ± 0.52	1.33 ± 0.49	1.38 ± 0.51

BoNT-A botulinum toxin type A, *JRS* Jankovic Rating Scale

Table 2 Clinical outcomes of the preseptal and pretarsal BoNT-A injections

	Preseptal injection	Pretarsal injection	*p* value
BoNT-A (total units)	18.75 ± 2.53	18.75 ± 2.27	1.000
Hemifacial spasm	18.39 ± 2.78	18.39 ± 2.46	1.000
Blepharospasm	20.00 ± 0.00	20.00 ± 0.00	1.000
BoNT-A (units per eyelid)	9.56 ± 1.12	9.56 ± 1.12	1.000
Hemifacial spasm	9.44 ± 1.24	9.44 ± 1.24	1.000
Blepharospasm	10.00 ± 0.00	10.00 ± 0.00	1.000
Latency to response (days)	8.63 ± 7.33	5.85 ± 3.50	0.014
Hemifacial spasm	8.68 ± 7.13	6.16 ± 3.69	0.058
Blepharospasm	8.44 ± 8.44	4.78 ± 2.63	0.043
Latency to the peak of efficacy (days)	20.43 ± 13.92	16.38 ± 11.45	0.019
Hemifacial spasm	20.87 ± 14.46	16.74 ± 11.55	0.026
Blepharospasm	18.89 ± 12.53	15.11 ± 11.71	0.551
Duration of response (weeks)	9.63 ± 1.78	10.48 ± 1.78	0.005
Hemifacial spasm	9.74 ± 1.93	10.32 ± 1.89	0.045
Blepharospasm	9.22 ± 1.09	11.00 ± 1.32	0.040
Post-treatment JRS (1–4)	1.58 ± 0.55	1.18 ± 0.39	0.000
Hemifacial spasm	1.55 ± 0.57	1.23 ± 0.43	0.018
Blepharospasm	1.67 ± 0.50	1.00 ± 0.00	0.014
Self-response scale (at 1 month −1–5)	3.48 ± 0.71	3.83 ± 0.59	0.018
Hemifacial spasm	3.48 ± 0.72	3.84 ± 0.64	0.045
Blepharospasm	3.44 ± 0.73	3.78 ± 0.44	0.180
Self-response scale (at 3 months −1–5)	3.35 ± 0.70	3.68 ± 0.62	0.007
Hemifacial spasm	3.39 ± 0.76	3.71 ± 0.64	0.025
Blepharospasm	3.22 ± 0.44	3.56 ± 0.53	0.083
Satisfaction rating scale (at 1 month 0–10)	7.38 ± 1.64	8.28 ± 1.30	0.001
Hemifacial spasm	7.39 ± 1.69	8.13 ± 1.36	0.018
Blepharospasm	7.33 ± 1.58	8.78 ± 0.97	0.010
Satisfaction rating scale (at 3 months 0–10)	7.20 ± 1.52	8.15 ± 1.27	0.000
Hemifacial spasm	7.16 ± 1.57	8.06 ± 1.34	0.002
Blepharospasm	7.33 ± 1.41	8.44 ± 1.01	0.008

BoNT-A botulinum toxin type A, *JRS* Jankovic Rating Scale

Discussion

Despite the fact that BoNT-A injections have been widely used as the treatment of choice in HFS and BEB, a general injection technique and dosage have been lacking. Aramideh et al. reported the beneficial effects of additional injections at the upper lateral and medial PT portion of the OOM into the regular orbital injections for the treatment of BEB regardless of clinical features [14]. Jankovic also observed the same benefit of the PT injections in his large long-term experience as well as in a single-blind controlled study, using the PT injections at the right eye and the PS injection at the left eye in patients with BEB. The study demonstrated no difference in the response rate between the two techniques, but significantly higher rate of ptosis observed in the PS side [16]. Albanese et al. reported a greater efficacy of the sole PT injections than the conventional orbital part of OOM in patients with BEB who failed to benefit from the standard orbital injections [13]. Furthermore, Esposito et al. expanded these notions as it found a benefit of combined injection technique without increasing the dose in patients with either primary or secondary resistance to the conventional orbital injections as well as in patients with atypical presentation characterized by the levator palpebrae inhibition phenomenon or eyelid opening apraxia [21]. In contrast to numerous published studies on BEB, only a few retrospective studies were evaluated in patients with HFS [15, 22]. Cakmur et al. and Sorgun et al. reported higher response rate with longer duration of maximum response and fewer major side effects with the PT injections in patients with HFS which were consistent with our study. However, the average dose of BoNT-A in their PT injection group was relatively higher than that of the PS injection group [15, 22].

Our findings confirm the greater efficacy of the BoNT-A injection at the PT portion over the conventional orbital

Table 3 Complications of preseptal and pretarsal injections of BoNT-A in patients with hemifacial spasm or blepharospasm

	Preseptal injections $n = 40$	Pretarsal injections $n = 40$	Total sessions $n = 80$
Total complications	10 (25.0%)	5 (12.5%)	13 (18.0%)
Major complications			
Ptosis/droopy eyelid	3 (7.5%)	0 (0.0%)	3 (3.8%)
Minor complications			
Tearing	2 (5.0%)	1(2.5%)	3 (3.8%)
Hematoma	1 (2.5%)	3 (7.5%)	4 (5.0%)
Irritation	4 (10%)	1 (2.5%)	5 (6.3%)

BoNT-A botulinum toxin type A

portion of the OOM which is demonstrated in this study as the PS injection for the treatment of HFS and BEB. Moreover, the PT injection technique produces a significantly higher response rate as well as patient satisfaction with lower frequency of major complications than the PS technique. The possible reason that the PT injection technique provides more efficacy than the PS injections is that the PT portion of the OOM is mainly mediating involuntary blinking of the eyelids, while the PS portion is mainly used for the forceful volitional eyelid closure [23, 24]. A recent study on the histologic compositions of the human OOM also showed that the PT portion had more skeletal muscle and neurons innervating the muscle fibers per surface area than the PS portion [23]. Furthermore, the PT portion consists mainly of type II muscle fibers which are relatively shorter in length than the PS portion [23, 25, 26]. Therefore, the BoNT-A that be directly injected into the PT portion could easily diffuse throughout the length of muscle fibers and reach all the neuromuscular junctions effectively with the minimum dose.

In patients with HFS, the average total dose of BoNT-A was about 18 units. The latency to response was not found to be statistically significantly different between both injection techniques, similar to the finding in the earlier studies [15, 22]. This result reflected a sustainable onset of action of the BoNT-A without an effect on injection sites. However, the latency to the peak of efficacy and duration of response were significantly better in the PT group. When compared with the earlier studies, the duration of response in our study was only 10 weeks, which is relatively shorter than others [15, 22]. This finding could be due to the low-dose technique used in our study. Anyhow, most of the patients were satisfied with our low-dose technique and pleased to receive an injection session on average every 3 months.

In patients with BEB, the average total dose of BoNT-A given in our patients was about 20 units, considerably lower than most of the previous studies [13–15]. The PT injections failed to demonstrate significant benefits in terms of latency to the peak of efficacy and self-response scale at 1 and 3 months compared to the PS injections. Also, the relative lack of efficacy of the PS injections compared to the PT injections regarding latency to response, duration of response, post-treatment JRS, and satisfaction rating scale might have resulted from the inadequate dose and number of injection sites. Long-term studies with a larger sample size are required to evaluate the efficacy and response rate of the low-dose injection techniques in patients with BEB.

Regarding complications, ptosis and droopy eyelid were observed only in the PS injection group which was similar to the previously published studies [13, 16]. This finding could be explained by the histological compositions of the PS portion that contain more adipose tissue and lack of denser deep tissue support [23]. Additionally, the distance between the PS injection sites is closer to the levator palpebrae muscle than the PT injection sites. Therefore, BoNT-A that is being directly injected into the PS portion could cause ptosis and droopy eyelid. Eyelid hematoma is the main complication related to the PS injections, owing to numerous capillaries in the subdermal plexus. If bleeding is observed during the injection, immediate and gentle compression for about 3 minutes is recommended.

We acknowledge that our present study has some limitations. First, our study based on one center and the BEB subgroup population was too small to draw a definite conclusion. A multicenter trial with a larger sample of BEB patients is required to evaluate the therapeutic efficacy. Second, even the patients and the evaluator were unaware of which technique that had been injected by the injector, some patients might notice the differences during the injection sessions. Also, the PT injections are more painful and easily cause bruising and local hematoma than the PS injections. These possibly cause some biased information from the patients according to their preference. Last, the clinical efficacy of the treatment was partly evaluated by subjective data obtained from patient symptom diaries and follow-up phone interviews whose confounding factors were difficult to control. However, we used a crossover design to reduce the influence of confounding covariates that could affect the results of the study.

In conclusion, our findings suggested that the low-dose BoNT-A injection at the PT portion of the OOM provides more efficacy, safety, and patient satisfaction than the PS

portion for the treatment of involuntary eyelid twitching in patients with HFS and could benefit for patients with BEB. We recommend using this technique in the treatment of HFS and BEB to improve the clinical efficacy and reduce costs of treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards." This study was approved by the Institutional Review Board of the hospital, and informed consent was obtained from the study participants.

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