ORIGINAL ARTICLE

Efficacy and Complications of Full Dose versus Half Dose of Botulinum Toxin Type A Injection in Benign Essential Blepharospasm

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Objective: To compare the effectiveness, patient satisfaction, and complications associated with pretarsal botulinum toxin type A (BTX-A) injections using half versus full doses of benign essential blepharospasm (BEB).

Materials and Methods: A prospective double-masked randomized control trial was conducted in 20 patients. Each patient was randomized to receive either 40 or 80 units of BTX-A injections at Thammasat Hospital between April 2022 and August 2023. The primary outcome measures were frequency and severity using the Jankovic Rating Scale (JRS), latency to response, self-response scale, and patient satisfaction scale at four weeks and 12 weeks post-injection. The secondary outcome measures were complications of injection in each visit.

Results: There were no significant differences between the groups receiving half-dose and full-dose BTX-A injections in the self-response scale at 2.60±0.52 versus 2.00±1.15, (p=0.277), patient satisfaction scale at 8.30±1.57 versus 7.00±1.49, (p=0.063) at four weeks and JRS frequency at 1.00±0.82 versus 1.20±0.92, (p=0.687), JRS severity at 1.30±1.16 versus 1.40±0.97, (p=0.784), latency to response at 5.80±1.99 versus 6.80±1.93, (p=0.214), self-response scale at 2.70±0.48 versus 2.20±0.63, (p=0.067), and patient satisfaction scale at 8.10±1.60 versus 8.30±1.49, (p=0.776) at 12 weeks. Complications, including epiphora, dry eye, and lagophthalmos, were observed in both groups.

Conclusion: The present study indicated no significant differences between half-dose and full-dose BTX-A injections. Either dose showed comparable efficacy and safety in treating BEB.

Trial registration: The present study protocol was registered at the Thai Clinical Trials Registry (TCTR20240320002; date March 20, 2024).

Keywords: Botulinum toxin type A, Benign essential blepharospasm, Jankovic Rating Scale

Received 11 April 2024 | Revised 13 August 2024 | Accepted 20 August 2024

J Med Assoc Thai 2024;107(10):778-85

Website: http://www.jmatonline.com

Benign essential blepharospasm (BEB) is an uncommon form of focal cranial dystonia, manifesting as involuntary contractions of orbicularis oculi muscles. In 2011, Bhidayasiri et al. reported the prevalence of BEB at 1.6 out of every 10,000 individuals at an academic tertiary referral center among Thai patients who came from the southern part of Bangkok[1]. It typically presents during the age range of the fifth to seventh decades, with a greater prevalence among females than males. This is a chronic condition that develops gradually, leading to repetitive muscle contractions around the eyes, causing uncontrollable and frequent blinking on the bilateral side. If left untreated, the symptoms can worsen in intensity and frequency, potentially advancing to eyelid closure, impact on psychiatric health, intellectual capabilities, and eye symptoms[2,3].

Botulinum toxin type A (BTX-A) is preferred over treatments like oral medications because it can provide relief for 10 to 12 weeks when administered properly and the side effects are short-lived. Despite the need for repeated injections, it remains the treatment of choice compared to oral medications. A commonly used treatment involves injecting BTX-A directly into the orbicularis oculi muscle. This approach has shown both effectiveness and safety over extended periods[4]. Typically, the recommended dose of abobotulinumtoxin A (Dysport®) injected for treatment of BEB is 80 units per eye with an average treatment interval of three to four months[5]. Previous studies in Thailand have shown that lower

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How to cite this article:

Thitiwichienlert S, Sirikietsoong P, Lolekha P, Sapthanakorn W. Efficacy and Complications of Full Dose versus Half Dose of Botulinum Toxin Type A Injection in Benign Essential Blepharospasm. J Med Assoc Thai 2024;107:778-85.

DOI: 10.35755/jmedassocthai.2024.10.778-785-897

doses of BTX-A are as effective as normal doses in patients with blepharospasms and hemifacial spasms (HFS)[6,7]. The authors hypothesized that reducing the dose of BTX-A could reduce various side effects while still providing efficacy that was not inferior to normal injections. In the present study institute, the authors conducted a prospective comparison between two dosing regimens of Dysport® injection for treating BEB, a half dose of 40 units and a standard dose of 80 units.

Materials and Methods

The study was approved by the Medical Ethics Committee of Thammasat University (MTU-EC-PE-1-045/65), Pathum Thani, Thailand, and was conducted in accordance with the tenets of the Declaration of Helsinki. A prospective, randomized, double-blind, placebo-controlled trial was carried out between April 2022 and August 2023 at the Botulinum Toxin Clinic located at Thammasat University Hospital, Pathum Thani, Thailand. The study enrolled patients diagnosed with BEB by either a neuro-ophthalmologist or neurologist who had received the most recent BTX-A injection for over three months. The diagnosis of BEB was determined using diagnostic criteria from a prior study, which demonstrated a sensitivity of 88% to 92% and a specificity of 79% to 83%[8]. Pertinent demographic information of each participant was collected along with their pre-treatment Jankovic Rating Scale (JRS). Exclusion criteria encompassed individuals with a documented allergic response to BTX-A and patients displaying other craniofacial dyskinesia conditions such as apraxia of lid opening or facial synkinesis. Prior to participation, all individuals provided written informed consents.

First, the authors had very few subjects to enroll, by generated publicity for the trial by outlining the benefits of participating in the local eye clinic and among various specialty clinics. Moreover, the authors urged the patients to share their experiences. If anyone exhibited similar symptoms, they were encouraged to come for an examination. Once a qualified subject was identified, the subject was enrolled. When the eligibility criteria were met, the patients were assigned to either a control group or study group by using the block randomization method, a block size of 4 for a randomized block procedure. The possible combinations with 2 H (half-dose) and 2 F (full-dose) subjects could be assigned as follows: HHFF, HFHF, HFFH, FHHF, FHFH, FFHH. Blocks would be randomly selected to determine the assignment of all participants as HHFF, HFHF, HFFH, FHHF, FHFH, FFHH. This procedure concluded with all participants each was in both the half-dose and full-dose groups. In the control group, a full dose of Dysport® was injected into the pretarsal portion of the orbicularis oculi muscle, with 10 units at each injection point, resulting in a total dose of 80 units, or 40 units per eye. In the study group, a half dose of Dysport® was administered into the same muscle's pretarsal part, utilizing 5 units at each injection point, resulting in a total dose of 40 units or 20 units per eye. The primary outcome measures were frequency and severity using the JRS, latency to response, self-response scale, and patient satisfaction scale at 4 weeks and 12 weeks post-injection. The secondary outcome measures were complications of injection in each visit.

Pretarsal injection procedure

BTX-A pretarsal injection was performed by a single neuro-ophthalmologist (ST) in the present study tertiary care academic institution. After preparation of abobotulinumtoxin A (Dysport®) (500 units per vial IPSEN, Boulogne Bilancourt, France), stored at temperatures between 2°C to 8°C. The substance was diluted using 2.5 mL of 0.9% normal saline solution to achieve a concentration of 200 units per mL, equivalent to 20 units per 0.1 mL. In the full-dose group, 0.4 mL, or 80 units, was drawn into a 1 mL syringe, followed by the addition of 0.4 mL of 0.9% normal saline solution, yielding 80 units in 0.8 mL, or 10 units of 0.1 mL. The mixture was then divided into eight injection sites (Figure 1). In contrast, for the half dose group, 0.2 mL, or 40 units, was drawn into a 1 mL syringe, followed by the addition of 0.6 mL of 0.9% normal saline solution, resulting in 40 units in 0.8 mL, or 5 units of 0.1 mL. The research assistant was the person who prepared the drug and concealed the dose of BTX-A injection by using the same syringe and needle gauge. The principal investigator (ST) administered the injections, and the patients were blinded to whether they were in the full dose or half dose group. A co-investigator (PS) generated the random allocation sequence, enrolled participants, and another co-investigator (WS) assigned participants to interventions.

Before the injection was administered, all participants were interviewed to ascertain the presence of symptoms such as tearing, ptosis, lagophthalmos, and irritation. The severity of blepharospasm was defined by the JRS[9,10] as grade 0 for no spasm, grade 1 for minimal, increased blinking present only

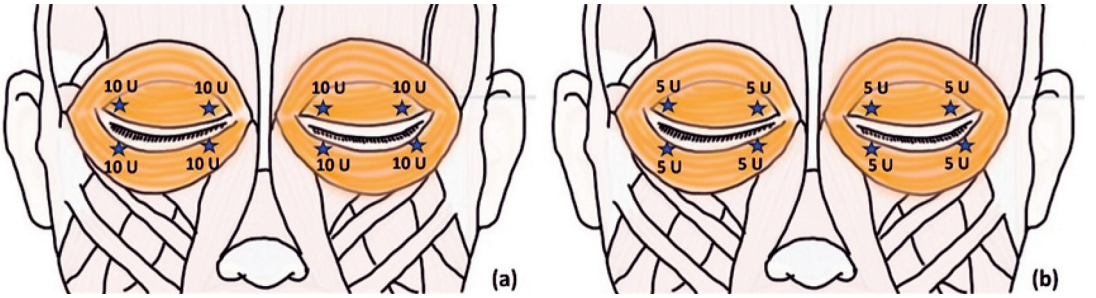

Figure 1. shows the pretarsal injection technique of Botulinum toxin type A in (a) the control group and (b) the study group.

with external stimuli, grade 2 for mild, spontaneous eyelid fluttering without functional impairment, grade 3 for moderate spasm with mild incapacitating spasm, and grade 4 for severe incapacitating spasm. The frequency of blepharospasm was also defined by the JRS as grade 0 for no spasm, grade 1 for slightly increased frequency of blinking, grade 2 for eyelid fluttering lasting less than one second, grade 3 for eyelid spasm lasting more than one second, but eyes open more than 50% of the waking time, and grade 4 for persistent eyelid spasm more than 50% of the waking time.

Follow-up visits

At four weeks and 12 weeks post-injection, participants were re-interviewed, and their JRS was assessed by a principal investigator blind to the patient grouping at the clinic. According to the previous studies[11,12], the authors defined the latency to response as equal to the onset of the patient's perception of a reduction in eyelid spasm, and the latency to the peak of efficacy equal to the onset at which the patient had no longer perceived any eyelid spasm. Regarding the self-response and satisfaction scales, participants were requested to rate their condition using an analog scale, ranging from –1 indicating worsening, to 3 indicating marked response, and a numeric satisfaction scale ranging from 0, indicating dissatisfaction, to 10, indicating high satisfaction.

Statistical analysis

Sample size was calculated using the two independent methods. Statistical analyses were performed by using the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, USA). Baseline characteristics were described as number (percentage), median (range), and mean with standard deviation (SD). Chi-square or Fisher's exact test was employed to compare proportions between the study groups, independent t-test was used to compare the means of the two groups, and Mann-Whitney U test was used for non-normal distributions. All reported p-values were 2-sided with p-value less than 0.05 set as the threshold for statistical significance. Independent t-test or Mann-Whitney U tests were used to compare the means or medians of the two groups as appropriate. Chi-square or Fisher's exact test was used as appropriate for comparing proportions. The level of statistical significance was set at p-value less than 0.05. The chi-square and Fisher's exact tests were used to compare categorical variables, and an independent t-test was used to analyze continuous variables for normal distribution. Mann-Whitney test was used for non-nominal distributions.

The analysis was initially masked, and dose of treatment was made unknown to participants, care providers, investigators, and outcome assessors. The present study protocol was registered in the Thai Clinical Trials Registry (TCTR) and approved by TCTR Committee on 20 March 2024, identification number: TCTR20240320002. Data of all cases in the analyses are available on request (the trial protocol can be accessed at https://www.thaiclinicaltrials.org/show/TCTR20240320002).

Results

Twenty patients, or 40 eyes, were included in the present study. The mean age was 66.45±10.41 years, with a range of 50 to 87 years. All patients were female, demographic data, duration of disease, duration of previous BTX-A injection, and pre-treatment JRS score of severity and frequency at enrollment were not significantly different in both groups (Table 1). Figure 2 shows the participant flow diagram of the study process. The comparison between groups receiving half-dose and full-dose of BTX-A revealed no statistically significant differences in terms of latency to response at 5.80±1.99 versus 6.80±1.93, (p=0.214), latency to the peak of efficacy

Table 1. Comparison of patient's baseline characteristics between control and study group

	Total (n=20)	Control group; full dose of BTX-A (n=10)	Study group; half-dose of BTX-A (n=10)	p-value
Sex (female); n (%)	20 (100)	10 (100)	10 (100)	-
Age (years); median (min-max)	64.5 (50 to 87)	62.5 (50 to 87)	67.5 (51 to 87)	0.237
Duration of disease (years); median (IQR)	5.0 (4.0 to 5.0)	4.5 (3.0 to 5.0)	5.0 (4.0 to 5.25)	0.319
Duration of previous BTX-A (months); median (IQR)	5.0 (4.0 to 5.0)	4.0 (3.0 to 5.75)	5.0 (4.0 to 5.75)	0.252
Pre-treatment JRS score (severity); mean±SD	2.00±0.92	2.00±0.82	2.00±1.05	0.873
Post-treatment JRS score (severity); mean±SD	1.35±1.04	1.30±1.16	1.40±0.97	0.784
Pre-treatment JRS score (frequency); mean±SD	1.95±0.89	2.10±0.88	1.80±0.92	0.497
Post-treatment JRS score (frequency); mean±SD	1.10±0.85	1.00±0.82	1.20±0.92	0.687

BTX-A=botulinum toxin type A; JRS=Jankovic Rating Scale; IQR=interquartile range; SD=standard deviation
p-value from independent t-test or Mann-Whitney U test

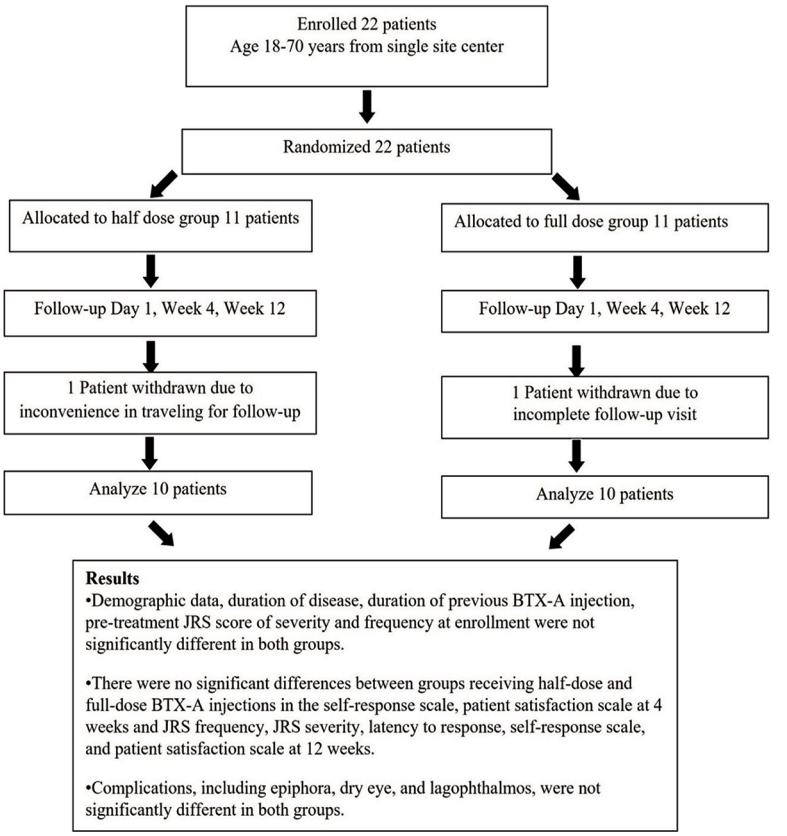

Figure 2. shows the participant flow diagram of the study process.

at 11.20±6.76 versus 12.30±4.35, (p=0.304), JRS severity at 12 weeks post-treatment at 1.30±1.16 versus 1.40±0.97, (p=0.784), JRS frequency at 12 weeks post-treatment at 1.00±0.82 versus 1.20±0.92, (p=0.687), the self-response scale at four weeks at 2.60±0.52 versus 2.00±1.15, (p=0.277), and 12 weeks at 2.70±0.48 versus 2.20±0.63, (p=0.067). The satisfaction rating scale at four weeks at 8.30±1.57 versus 7.00±1.49, (p=0.063) and 12 weeks at 8.10±1.60 versus 8.30±1.49, (p=0.776). A summary of the results for both doses is presented in Table 2. Figure 3 shows the changes in JRS following injection over time.

Regarding injection-related complications, minor complications including epiphora were observed in 25% of patients at four weeks post-injection and in 20% of patients at 12 weeks post-injection. Dry eye was reported by 20% of patients

Table 2. Primary outcomes between control and study group

	Total (n=20); mean±SD	Control group; full dose of BTX-A (n=10); mean±SD	Study group; half-dose of BTX-A (n=10); mean±SD	p-value
Latency to response (days)	6.30±1.98	5.80±1.99	6.80±1.93	0.214
Latency to the peak of efficacy (days)	11.75±5.56	11.20±6.76	12.30±4.35	0.304
4 weeks Post-treatment JRS score (severity)	0.80±1.06	0.50±0.71	1.10±1.29	0.338
12 weeks Post-treatment JRS score (severity)	1.35±1.04	1.30±1.16	1.40±0.97	0.784
4 weeks Post-treatment JRS score (frequency)	0.65±0.99	0.30±0.48	1.00±1.25	0.211
12 weeks Post-treatment JRS score (frequency)	1.10±0.85	1.00±0.82	1.20±0.92	0.687
Self-response scale (at 4 weeks)	2.30±0.92	2.60±0.52	2.00±1.15	0.277
Self-response scale (at 12 weeks)	2.45±0.60	2.70±0.48	2.20±0.63	0.067
Satisfaction rating scale (at 4 weeks 0 to 10)	7.65±1.63	8.30±1.57	7.00±1.49	0.063
Satisfaction rating scale (at 12 weeks 0 to 10)	8.20±1.51	8.10±1.60	8.30±1.49	0.776

BTX-A=botulinum toxin type A; JRS=Jankovic Rating Scale; SD=standard deviation
p-value from independent t-test or Mann-Whitney U test

Table 3. Secondary outcomes between control and study group

	Total (n=20); n (%)	Control group; full dose of BTX-A (n=10); n (%)	Study group; half dose of BTX-A (n=10); n (%)	p-value
Ptosis				
At 4 weeks	3 (15.0)	2 (20.0)	1 (10.0)	1.000
At 12 weeks	2 (10.0)	1 (10.0)	1 (10.0)	1.000
Lagophthalmos				
At 4 weeks	3 (15.0)	2 (20.0)	1 (10.0)	1.000
At 12 weeks	2 (10.0)	1 (10.0)	1 (10.0)	1.000
Epiphora				
At 4 weeks	5 (25.0)	3 (30.0)	2 (20.0)	1.000
At 12 weeks	4 (20.0)	2 (20.0)	2 (20.0)	1.000
Dry eye				
At 4 weeks	4 (20.0)	2 (20.0)	2 (20.0)	1.000
At 12 weeks	2 (10.0)	1 (10.0)	1 (10.0)	1.000

BTX-A=botulinum toxin type A
p-value from Fisher's exact test

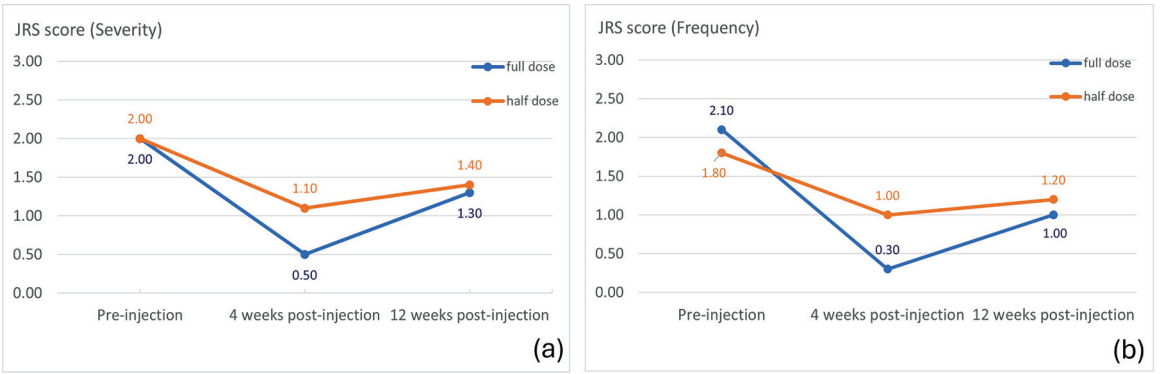

Figure 3. shows the changes in JRS (a) severity and (b) frequency following injection over time.

at four weeks post-injection and by 10% of patients at 12 weeks post-injection. Major complications including ptosis and lagophthalmos occurred in 15% of patients at four weeks post-injection and in 10% of patients at 12 weeks post-injection. Notably, there were no statistically significant differences between the two groups concerning these complications, as demonstrated in Table 3.

Table 4. Comparison of previous literature studies and the present study

Literature	No. of BEB cases	Study design	Study group	Primary outcomes	Results
Truong D, et al. (2008)	120	A randomized, double-blind, placebo-controlled trial	Control group (placebo) vs. Study groups (40, 80, 120 units/eye) of abobotulinumtoxin A (Dysport®)	The percentage of normal activity (PNA) on the BDS (the difference in median PNA between active treatment and placebo; 95% confidence intervals) at 4 weeks post-injection	BTX-A 80 units/eye provide the best balance of sustained efficacy combined with a favorable safety profile and could be an appropriate starting dose for patients with BEB
Boyle MH, et al. (2009)	16	A randomized clinical trial	Control group (low dose 10 units/mL) vs. Study group (high dose 100 units/mL)	Pain score, Complications (ptosis, diplopia, tearing, and dry eye), Duration of relief	The study group showed a 58% reduction in perceived pain (1.94 vs. 4.59, p<0.001)
Poonyathalang A, et al. (2005)	7	Retrospective case series	Low dose (1.25 units per 0.1 mL) of onabotulinumtoxin A (Botox®)	Duration of efficacy (duration of action and interval between injections)	The low dose of BTX-A was sufficient to decrease the clinical symptoms of spasms with fewer side effects
The present study	20	A randomized, double-blind, placebo-controlled trial	Control group (full dose 80 units/eyes) vs. Study group (half dose 40 units/eyes) of abobotulinumtoxin A (Dysport®)	JRS, latency to response, self-response scale, and patient satisfaction scale at 4 weeks and 12 weeks post-injection	No significant differences between half-dose and full-dose BTX-A injections in efficacy and safety

BEB=benign essential blepharospasm; BTX-A=Botulinum toxin type A; JRS=Jankovic Rating Scale

Discussion

In 2008, Truong et al. compared the efficacy and safety of injections of 40, 80, and 120 units of Dysport® with placebo in BEB patients. They found that a starting dose of 80 units per eye was suitable for BEB, which was then utilized as a baseline for the control group in the present study[13]. In 2009, Michael et al. studied the efficacy of highly concentrated injections of BTX-A at 100 units per mL versus dilute doses of 10 units per mL in 16 patients with BEB. They found statistically significant reduction in pain scores at the side injected with a higher concentration compared to the other side injected with dilute concentration in the same patient while the treatment efficacy was not different[14]. Poonyathalang et al. compared the efficacy of low-dose (4 to 6.25 units per eye) of preseptal injections of onabotulinumtoxin A (Botox®) versus normal dose (12.5 to 25 units per eye) in a case series of seven patients with BEB and 26 patients with HFS. It showed that complete spasm relief was achieved in more than half of all patients[6]. Rojanapitayakorn et al. compared the efficacy of 75% low-dose (average dose of 46.1 units) injections of abobotulinumtoxin A (Dysport®) versus normal dose (average dose of 65.3 units) in a randomized single-blinded trial of 69 patients with HFS. It showed no significant differences in the treatment efficacy between the two groups[7]. That study also demonstrated the benefit of saving costs for patients. The present study results were compared with the previous studies on BEB patients in Table 4.

Key aspects of BTX-A treatment include the accurate concentration of the drug, the precise site of injection, and the technique employed for administering the injection. Due to the need for frequent and prolonged injections, the patient could potentially face the risk of immune responses, including the development of neutralizing antibodies. Such reactions might lead to the treatment becoming ineffective over time[15]. Moreover, a greater dosage is associated with an increased risk of post-injection side effects, such as ptosis and lagophthalmos[13]. Currently, the cost of BTX-A used in Thailand remains high, and it is not covered for patients with BEB. This limitation results in many blepharospasm patients having restricted access to BTX-A treatment. To lessen complications and lower expenses, the authors compared the efficacy and complications between the two dosing regimens of Dysport® injection.

In the present study, the authors chose abobotulinumtoxin A (Dysport®) because the drug has smaller molecules that are more likely to disperse better, so using a low dose may be beneficial. In terms of injection techniques, Lolekha et al. compared preseptal and pretarsal BTX-A injection techniques and found that low-dose injections at the pretarsal portion provide more efficacy, patient satisfaction, and fewer complications than the preseptal injections in BEB and HFS[11]. Therefore, the authors selected the pretarsal injection technique.

For demographic data, the two groups exhibited similar age ranges, disease duration, and time

since the last BTX-A injection. The present study findings reveal that half-dose and full-dose BTX-A pretarsal injections led to significant improvements in symptom severity and frequency, as indicated by the JRS scores after treatment at 2.00±0.82 versus 1.35±1.04, (p=0.015), and 1.95±0.89 versus 1.10±0.85, (p=0.002), respectively. It was believed that patients who were administered the full-dose BTX-A would experience longer-lasting effectiveness than those who received the half-dose. However, it was discovered that at 12 weeks, the JRS scores were comparable in both groups, with a more significant difference observed at four weeks following injection. If extending the follow-up period to 16 weeks, treatment efficacy may be maintained longer in the full dose group. Furthermore, the mean JRS score of the patients in the present study was quite low. Both groups' JRS scores were grade 2. It is unclear if the efficacy of the treatment would be affected by the severity of the disease, specifically JRS grade 3 or 4.

The satisfaction rating scale is a subjective measure that allows patients to self-evaluate. Factors influence the ratings given including age and the number of injections. There have been no studies investigating the impact of age on the desirability of BTX-A injections for the treatment of HFS. However, a previous study has found that age affects satisfaction rating scales, as older patients have higher satisfaction expectations for other treatments[16]. New cases of injections typically receive better satisfaction evaluation scores compared to cases necessitating repeated injections. The present study did not conduct a subgroup analysis to determine the age group, nor did it distinguish between repeated injections and new cases. However, it is interesting that the satisfaction rating scale at four weeks post-injection is nearly significant (p=0.063), probably because it is precisely the time of the drug's maximum effect that makes satisfaction the greatest than the 12 weeks. The incidence of complications was low in both groups. The complications of the full-dose group should be greater than those of the half-dose group, especially during the first four weeks post-injection. The authors have found unexpected results in the present study and believe that certain questions may be subjective. For instance, patients may find it challenging to report epiphora as they may confuse it with tearing caused by other conditions. However, the authors can objectively measure complications, such as dry eye, lagophthalmos, and ptosis. Therefore, the authors believe that it is possible to measure certain complications.

There were limitations to the present study. Recruitment of the case was difficult because of the low incidence of BEB. A small sample size and heterogeneity in disease severity made it difficult to apply to patients with more severe disease. In addition, the short-term follow-up made it difficult to make distinctions between the two groups in terms of long-term outcomes such as the frequency of repeated injections. The authors suggested that future studies should be the large cohorts with severe cases to explore the impact of long-term follow-up.

In conclusion, the present study indicates no significant differences between half-dose and full-dose BTX-A injections. Either dose shows comparable efficacy and safety in treating BEB.

What is already known on this topic?

Currently, there is no cure for BEB, but there are effective options to alleviate the frequency and severity of symptoms. The BTX-A is also the mainstay treatment because it is non-invasive and safe. There are commercial drugs that can be used in a variety of applications. Mixing the dose and injection site, as well as injection techniques are important to achieve the expected therapeutic effect.

What does this study add?

This study showed that injection of BTX-A in BEB patients revealed no difference in the effect of half dose versus full dose, which would be useful in reducing the cost of the patients while still having effective treatment results.

Acknowledgement

The authors would like to thank Miss Manussanun Tanavikrankoon for her support with the statistical analyses.

Ethics approval and consent to participate

The present study protocol was approved by the Medical Ethics Committee of Thammasat University (MTU-EC-PE-1-045/65), Pathum Thani, Thailand on 30 March 2022 and renew on 30 March 2023 to 29 March 2024. The Thai names and the English names of the Ethics committee that approved the study were attached.

Authors' contributions

ST: conceptualization, methodology, data curation, investigation, resources, writing-original draft, writing-review & editing, formal analysis, software, supervision, project administration, funding

acquisition. PS: conceptualization, methodology, investigation, resources, writing-original draft, formal analysis, software. PL: conceptualization, methodology, investigation, resources, writing-review & editing, supervision. WS: conceptualization, methodology, investigation, resources

Funding disclosure

The present study was funded by the Faculty of Medicine, Thammasat University.

Conflicts of interest

The authors declare that there is no conflict of interest.

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