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ORIGINAL ARTICLE

Long-term treatment of blepharospasm with botulinum toxin A: a service-based study over a 16-year follow-up in southern China

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Abstract

Objective To elucidate the effect of long-term treatment with botulinum toxin A (BTX-A) for blepharospasm. Prevalence data and clinical features in southern China and influencing factors for selecting BTX-A treatment were explored.

Methods We collected data retrospectively from 338 consecutive patients diagnosed with blepharospasm over 16 years to assess prevalence data and clinical features. Thereafter, all patients were classified into BTX-A (n = 135) or non-BTX-A (n = 203) treatment groups according to the patients' requests in order to explore the factors influencing whether BTX-A treatment was chosen. Furthermore, dynamic follow-up data were analyzed to evaluate the long-term efficacy in the BTX-A group.

Results The prevalence was 23.3 per million, with an onset age of 50.3 ± 12.3 years and a female:male ratio of 2.4:1; the most common symptom was excessive blinking (91.2%). The symptom severity and psychological assessment scores were significantly decreased by treatment with BTX-A ($p < 0.01$), and there was no significant difference in response duration with the prolongation of BTX-A injections. Adverse events occurred 52 times (5.0%) among 1038 injections. The symptom severity and psychological assessment scores and the occurrence of eye-opening difficulty were higher, and medical expenses and the symptom tolerability rate were lower in the BTX-A group than in the non-BTX-A group ($p < 0.05$).

Conclusion The onset age was earlier than that in Western countries. However, starting BTX-A treatment early is justified, even though a higher dosage was needed to maintain reliable long-term efficacy. Additionally, symptom severity and medical expenses are the primary factors affecting whether patients select BTX-A treatment.

Keywords Blepharospasm · Long term · Botulinum toxin · Prevalence · China

Introduction

Blepharospasm is a focal movement disorder that was first described in the late nineteenth century and is associated with hyperactivity of the orbicularis oculi and other muscles around the eyes, leading to bilateral involuntary eyelid closure with a severity ranging from increased blinking frequency to functional blindness [1, 2]. Despite different pathophysiologies, all

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forms of blepharospasm share a multitude of clinical features, such as peak age of onset in the fifties and sixties, higher incidence among women, and a possible association with dystonia in other body parts [3]. Blepharospasm is one of the most common forms of adult-onset dystonia. To date, the reported prevalence is between 20 (Japan) and 133 (southern Italy) per million in different geographic areas [4, 5]. However, the prevalence data and clinical features in China remain unclear.

Despite various treatments including drug therapy (benzodiazepines, anticholinergics, baclofen, etc.) and surgical therapy, repeated intramuscular injection of botulinum toxin A (BTX-A) is considered the first-line drug treatment for blepharospasm, according to American and European treatment guidelines as well as expert consensus [6, 7]. However, given the low selection rate of BTX-A treatment in clinical practice for several reasons in developing countries, an exploration of the factors affecting the choice of BTX-A injection treatment is worthwhile. BTX-A is a potent bacterial exotoxin produced by the anaerobic bacteria *Clostridium botulinum* and can block the presynaptic release of acetylcholine, thus relieving muscle spasm [8]. Because motor end-plate function, nerve conduction, and muscle contraction force are gradually restored, repeated injections are needed [9]. At present, only two formulations of BTX-A (Botox and Prosigne) are licensed by the Chinese Food and Drug Administration for the treatment of blepharospasm in China. Blepharospasm is not life-threatening; nevertheless, it interferes with visual function and may even lead to functional blindness, such that quality of life may be significantly impaired with difficulty noted in work life and social life, or to marked anxiety or depression caused by dysfunction of the cortico-basal ganglia circuits [10, 11].

Several studies report that treatment of blepharospasm with BTX-A is associated with a positive impact on quality of life [12, 13]. Moreover, blepharospasm patients benefit from effective and safe treatment with BTX-A but may also suffer several adverse effects. To date, only a few large studies have focused on the dynamic effect of long-term BTX-A treatment for blepharospasm, examining aspects of clinical features (latency of effect, duration of effect, interval time, etc.) and adverse effects (ptosis, dry eye, diplopia, etc.) for all intervals as well as quality of life (anxiety, depression, Blepharospasm Disability Index, etc.) [14–16]. Therefore, this large, long-term study was designed to evaluate prevalence data and clinical features in southern China, to explore the factors influencing patients' selection of BTX-A treatment and to expand our knowledge of the effects of long-term therapy with BTX-A for blepharospasm.

Materials and methods

This retrospective study was approved by the institutional ethics committee of The First Affiliated Hospital, Sun Yat-sen University (2018-162). From January 1999 to January 2018, a total of 338 continuous blepharospasm patients (all from Guangzhou in southern China, an area with a population of 14,498,400 according to data from the National Bureau of Statistics in 2017) received treatment at Guangzhou Dystonia Center in The First Affiliated Hospital, Sun Yat-sen University, which is the best-known and largest clinical center for dystonia in southern China. All patients were classified into BTX-A (n = 135) or non-BTX-A (n = 203) treatment groups, according to the patients' request to select BTX-A treatment or not, to explore the factors affecting the selection of BTX-A treatment. Patients with concomitant chronic debilitating illness (organ failure, malignancies, etc.) or other movement disorders (Parkinsonism, chorea, etc.) were excluded (Fig. 1a).

BTX-A was provided by Botox (Allergan Inc., Irvine, CA, USA) or Prosigne (Lanzhou Institute of Biological Products, Lanzhou, China), and injections of the two formulations were performed at a 1:1 ratio. With informed consent, patients have the right to choose different types of BTX-A; therefore, the choice of BTX-A type was decided by patients. BTX-A was stored in a refrigerator according to the manufacturers' instructions and diluted with sterile sodium chloride solution to the concentration required (50 U/mL) 1 to 4 h before use. The standard treatment protocol was based on a brochure for

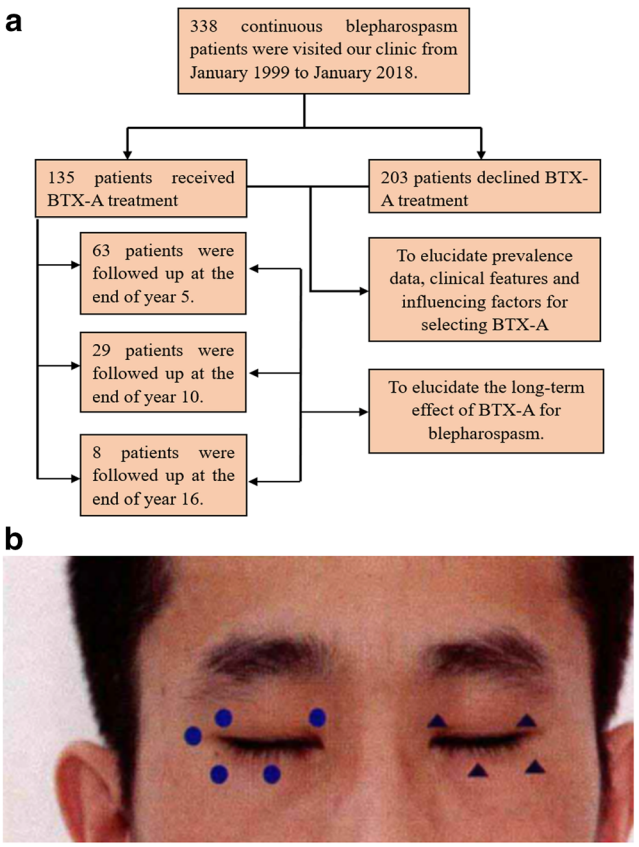

Fig. 1 Patient flow diagram (**a**) and location of injections for BTX-A treatment (**b**)

BTX injection (Fig. 1b) and was performed by experienced doctors. Normally, 2.5 to 5 units were used for each point, and 25 to 50 total units were used depending on spasm severity.

Clinical information (spasm severity and frequency, disease duration, duration of treatment, response latency, response duration, injection numbers, adverse effects, quality of life assessment, anxiety and depression scores) and general information (age, sex, family history, etc.) were collected retrospectively from medical records. The severity and frequency of blepharospasm are both graded on a 5-point scale from 0 (none) to 4 (severe) according to the widely used Jankovic Rating Scale (JRS) [17]. Assessment of quality of life was performed using the Blepharospasm Disability Index (BSDI) [17], a self-rating scale (0–4 points) ranging from "no impairment" or "slight-moderate-severe impairment" to "no longer possible due to my illness" and including 6 domains that affect quality of life. Symptoms of depression were assessed using the Self-Rating Depression Scale (SDS), with a higher score indicating more depression symptoms and no depression defined as a score less than 53. Symptoms of anxiety were evaluated using the Self-Rating Anxiety Scale (SAS), with a higher score indicating severe symptoms and no anxiety defined as a score less than 50.

The general and clinical information was used to obtain the prevalence data and clinical features in southern China and thereafter to explore the factors affecting whether patients selected BTX-A treatment. Furthermore, we analyzed the initial treatment and most recent follow-up data to elucidate the effect of long-term therapy with BTX-A for blepharospasm. Finally, we assessed follow-up data for each interval to determine the long-term effect of BTX-A on blepharospasm.

Statistical analyses

Descriptive statistics for continuous variables are presented as the means ± standard deviation, and categorical variables are presented as frequencies and percentages. We used Student's *t* test (normally distributed variables) or the *Z* test (non-normally distributed variables) to examine both groups of patients with regard to continuous variables, and we used the chi-squared test or Fisher's exact test to evaluate the patients regarding categorical variables. The threshold for significance was set at $p < 0.05$. Data were analyzed using SPSS 13.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

To date, 2080 patients have visited our dystonia center, and among them, 338 (16.25%) had blepharospasm. Its estimated prevalence is 23.3 per million (338/14.50 million), making it second only to hemifacial spasm. The prevalence data and clinical features are presented in Table 1. Of these blepharospasm patients, the mean age was 50.3 ± 12.3 years, and the female:male ratio was 2.4:1. The median duration of blepharospasm was 6.0 years, and the median time from onset to diagnosis was 2.0 years. Among the patients, 215 (63.6%) had received previous drug treatment (Artane, Baclofen, and Biazepam), while 5 patients (1.5%) had a family history of blepharospasm. The JRS severity score was 2.5 ± 0.5, and the JRS frequency was 2.5 ± 0.6; the SDS and SAS scores were 51.9 ± 8.7 and 51.0 ± 4.3, respectively. The most common symptoms were excessive blinking (91.7%) and eye-opening difficulty (90.2%).

All patients were classified into BTX-A (n = 135) or non-BTX-A (n = 203) treatment groups, according to the patients' request to select BTX-A treatment or not, to explore the factors affecting selection of BTX-A treatment. The JRS severity, JRS frequency, SDS and SAS scores, and the occurrence of eye-

Table 1 The prevalence data and clinical features of blepharospasm (BE)

Variable	Mean or frequencies	Variance or percentages
Prevalence data		
Onset age (years)	50.3	12.3
< 50	158	46.7
50–60	107	31.7
61–70	51	15.1
> 70	22	6.5
Female (*n*)	240	71.0
Male (*n*)	98	28.9
Duration of BE (years)	6.0	3.0–10.0
Follow-up duration (years)	4.0	2.0–6.0
Time from onset to diagnosis (years)	2.0	1.0–3.0
Previous drug treatment (*n*)	215	63.6
No previous treatment	119	35.2
Family history (*n*)	5	1.5
Clinical assessment (scores)		
JRS—severity	2.5	0.5
JRS—frequency	2.5	0.6
Self-Rating Anxiety Scale	51.0	4.3
Self-Rating Depression Scale	51.9	8.7
Clinical symptom (*n*)		
Excessive blink	310	91.7
Difficulty of eyes-opening	305	90.2
Photophobia	276	81.7
Eye strain	258	76.3
Dry eye	196	58.0
Blurred vision	269	79.6
Ptotic sensation	288	85.2
Periocular abnormal sensation	125	37.0

opening difficulty were significantly higher, while medical expenses and symptom tolerability were significantly lower in the BTX-A group than in the non-BTX-A group ($p < 0.05$, Table 2).

In the BTX-A group, a total of 1038 injections were applied, the mean response latency was 3.9 ± 2.3 days, and the mean response duration was 4.0 ± 1.7 months. The clinical assessment scores (JRS severity, JRS frequency, SDS, SAS and BSDI) were significantly decreased by treatment with BTX-A ($p < 0.01$), suggesting that BTX-A can improve physical symptoms as well as anxiety and depression. However, patients are currently receiving a higher dosage than at their first injection ($p = 0.000$). Among 1038 injections, adverse events occurred 52 times (5.0%), with no severe sequelae. Interestingly, the first injection group exhibited a higher rate of adverse events than the most recent injection group ($p = 0.001$, Table 3). To determine the long-term efficacy of BTX-A treatment, we analyzed the data for each interval. The response latency was significantly lengthened in the 10th ($p < 0.05$) and 11th ($p < 0.01$) years, and the dosages were significantly increased in the 5th ($p < 0.01$) year compared with those in the first year. Moreover, an obvious increase in the dosage occurred during the 9th year ($p < 0.01$). However, the response duration was not significantly decreased (Fig. 2), indicating that a higher dosage was needed to maintain reliable long-term efficacy.

Discussion

Blepharospasm is one of the most common forms of adult-onset dystonia and lacks an effective cure; the dynamic follow-up data shown in our article again suggested the long-term efficacy and safety of BTX-A treatment. Furthermore, the patients' selection rate of BTX-A treatment in clinical practice is low in our study; therefore, this study provides background information to reduce obstacles for promoting BTX-A application in the clinic. Additionally, the estimated prevalence and clinical features in southern China were also addressed to better understand blepharospasm.

To date, the reported prevalence of blepharospasm has been significantly different depending on the geographic area, which has not always been clearly indicated. In our study,

Table 2 The comparison of factors for patients' selection for BTX-A treatment between BTX-A group and non-BTX-A group

Variable	BTX-A $n = 135$	Non-BTX-A $n = 203$	X^2 or t value	p value
Age of onset (years)	51.5 ± 12.4	49.2 ± 12.6	1.649	0.100
Female (n)	95 (70.4)	145 (71.4)	0.044	0.834
Time from onset to diagnosis (years)	2 (1–3)	2 (1–3)	-	0.844
Effective of previous drug (n)	76 (58.5)	139 (67.0)	2.517	0.113
JRS—severity (scores)	2.8 ± 0.5	2.2 ± 0.4	13.238	0.000*
0–2 (n)	27 (20.0)	161 (79.3)	115.547	0.000*
3–4 (n)	108 (80.0)	42 (20.7)	115.547	0.000*
JRS—frequency (scores)	3.0 ± 0.5	2.1 ± 0.3	19.180	0.000*
0–2 (n)	18 (13.3)	189 (93.1)	217.363	0.000*
3–4 (n)	117 (86.7)	14 (6.9)	217.363	0.000*
SAS (scores)	43.8 ± 3.1	48.8 ± 3.0	14.980	0.000*
No anxiety (n)	10 (7.4)	115 (56.7)	84.361	0.000*
Mild anxiety (n)	112 (83.0)	87 (42.7)	53.863	0.000*
Moderate anxiety (n)	13 (9.6)	1 (0.5)	17.048	0.000*
Severe anxiety (n)	0 (0.0)	0 (0.0)	-	-
SDS (scores)	54.2 ± 7.3	50.5 ± 9.2	4.046	0.000*
No depression (n)	56 (41.5)	124 (61.1)	12.515	0.000*
Mild depression (n)	66 (48.9)	59 (29.1)	13.673	0.000*
Moderate depression (n)	9 (6.7)	14 (6.9)	0.007	0.934
Severe depression (n)	4 (3.0)	6 (3.0)	0.000	1.000
Fear of adverse effects (n)	48 (35.6)	124 (61.1)	21.142	0.000*
Difficulty of eyes-opening (n)	127 (94.1)	145 (71.4)	26.460	0.000*
Excessive blink (n)	125 (92.6)	178 (87.7)	2.104	0.147
Medical expenses (n)	25 (18.5)	61 (30.0)	5.683	0.017*
Symptom tolerability (n)	10 (7.4)	78 (38.4)	40.504	0.000*

*$p < 0.05$

Table 3 The comparison of efficacy and quality of life between first injection and most recent injection

Variable	First injection	Most recent injection	X^2 or t value	p value
Dosage (u)	32.3 ± 2.6	36.0 ± 7.4	5.576	0.000*
Response latency (days)	3.9 ± 3.2	3.9 ± 2.4	0.151	0.880
Response duration (weeks)	3.6 ± 1.9	4.0 ± 1.7	1.601	0.110
JRS—severity (scores)	2.8 ± 0.5	3.3 ± 0.4	7.704	0.000*
JRS—frequency (scores)	3.0 ± 0.5	3.3 ± 0.5	3.970	0.000*
SAS (scores)	54.3 ± 3.8	48.3 ± 3.3	13.887	0.000*
SDS (scores)	54.2 ± 7.3	43.6 ± 5.8	13.078	0.000*
Adverse events (n)	15 (11.1)	2 (1.5)	10.609	0.001*
BSDI (scores)				
Reading	2.7 ± 0.7	1.3 ± 0.8	15.257	0.000*
Driving	2.7 ± 1.4	1.8 ± 0.7	2.869	0.006*
Watching TV	1.9 ± 0.2	1.7 ± 0.7	11.785	0.000*
Shopping	2.6 ± 0.6	1.6 ± 0.8	11.350	0.000*
Doing everyday activity	2.4 ± 0.6	1.5 ± 0.8	10.285	0.000*
Walking	2.9 ± 0.8	2.1 ± 0.9	8.352	0.000*

*$p < 0.05$

the estimated prevalence was 23.3 per million (although the prevalence appears more like the recruitment ratio), which is consistent with reported prevalence rates ranging from 20 to 133 per million [4, 5]. Additionally, the reported incidence of blepharospasm is 4.6 cases per 100,000 to 1,000,000 per year [18, 19]. However, considering that most studies, including ours, use treatment-based data and that few patients with mild blepharospasm visit the hospital, the actual prevalence and incidence of blepharospasm are greatly underestimated.

Normally, age is closely associated with blepharospasm risk, with a mean peak onset between the ages of 50 and 70 years. The prevalence rates were 26.6 per 100,000 in the 5th to 6th decades, 31.9 per 100,000 in the 6th to 7th decades, and 74 per 100,000 beyond the 7th decade, according to a previous study [5], while our study included 158 patients (46.7%) from 50 to 70 years old. However, the same number of patients was less than 50 years old (Table 1), suggesting that the onset age in southern China is earlier than that in Western countries. Additionally, factors including family history, postural tremor, head or facial trauma, increased blinking, and prior history of eye disease may be associated with the development of blepharospasm [20, 21]. In our study, 5 patients (1.5%) had a family history of blepharospasm, which is less than that in previous reports, indicating that genetic background seems not to be a significant factor for this Chinese population; the other factors were not fully evaluated [22]. Blepharospasm shows a female preference [23] with a female:male ratio ranging from 1.6 to 3.3:1 [24], while our ratio was 2.45:1.

To date, no consistent theory has emerged to elucidate the pathology. However, a recent important theory is that the pathogenic mechanisms are the same as those underlying abnormal cortico-striato-pallido-thalamic loops. Moreover, the

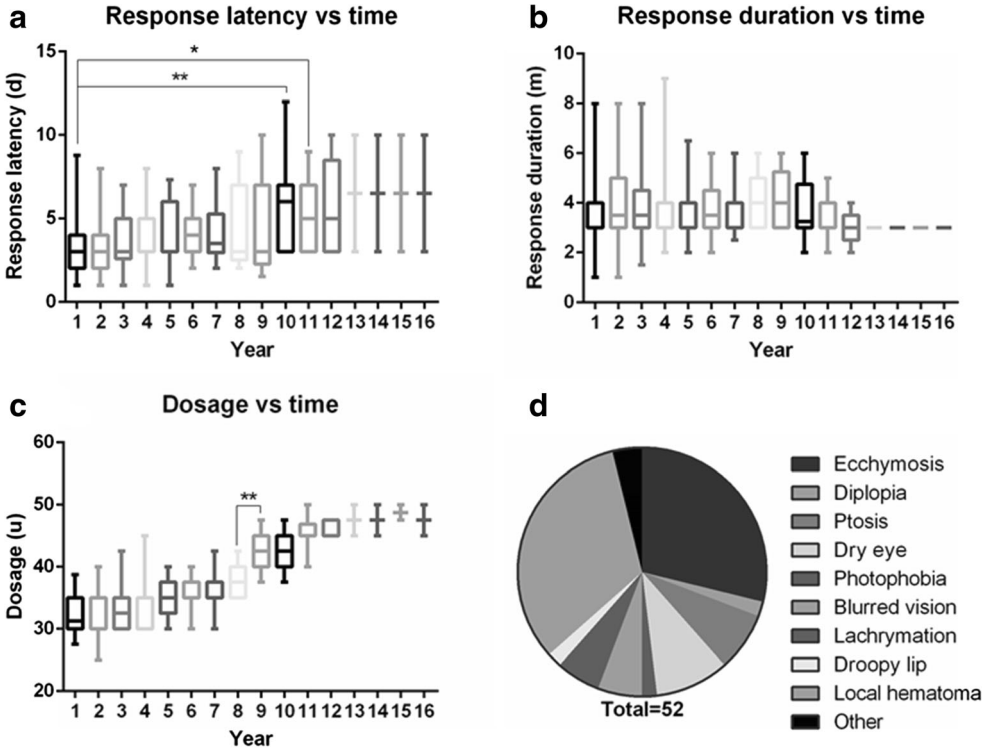

Fig. 2 The long-term efficacy of BTX-A treatment. The response latency was significantly lengthened in the 10th and 11th year (**a**), and the dosage was significantly increased in the 5th year compared with the first year. Moreover, an obvious increase in dosage occurred during the 9th year ($p < 0.01$, **c**). In addition, the response duration was not significantly decreased (**b**). Among the 1038 injections, adverse events occurred 52 times (5.0%) with no severe sequelae (**d**)

basal ganglia play an important role in blepharospasm, as a progressive decrease in dopamine levels in the basal ganglia may be associated with the development of blepharospasm, and the aging-related decrease in dopamine levels explains the peak onset between 50 and 70 years of age [14, 23, 25, 26]. The disease is sometimes difficult for physicians and patients to recognize due to the varied and non-specific symptoms of blepharospasm, especially in the case of mild blepharospasm. The incidence of symptoms in our study is similar to that in previous reports [22]; an average of 29 months are required to receive an accurate diagnosis, which is much longer than in previous reports [27], indicating that increased attention should be devoted to this area. To our knowledge, BTX-A is considered the first-line drug in the treatment of blepharospasm [6, 7, 28]. An increasing number of studies have demonstrated the efficacy and safety of BTX-A in the treatment of blepharospasm for improving the symptoms and quality of life [13, 16, 29, 30]. Only a few studies, however, have observed the effect of BTX-A on the treatment of blepharospasm dynamically, while our study again strongly supports the efficacy of BTX-A for the treatment of blepharospasm by not only comparing the initial treatment and the most recent follow-up data but also dynamically analyzing all follow-up data over 16 years. It is understandable that BTX-A improves motor symptoms by blocking the presynaptic release of acetylcholine and thus relieving muscle spasms and improving quality of life by reducing eyelid spasms. Interestingly, depression has been reported to be treated with BTX-A by injection into the glabellar region, which is based on the mechanism of the facial feedback hypothesis [11]. Indeed, dysfunction of cortico-basal ganglia circuits may be associated with mood and anxiety disorders; however, further studies are needed to better understand the mechanism.

Nevertheless, the selection rate of BTX-A treatment in developing countries was low (our BTX-A treatment rate was only 39.9%). Common reasons that account for the low usage rate include a lack of understanding of BTX-A treatment, fear of injections, difficulty in completing regular treatment, decision to choose another method of treatment, disagreement with the diagnosis, desire for further consultation, fear of adverse effects, and unknown reasons. To obtain a better understanding of the influencing factors, we analyzed data from blepharospasm patients who did or did not select BTX-A treatment, and the results indicate that whether BTX-A treatment was selected in clinical practice was somehow dependent on symptom severity and medical expenses. Due to the high price of Botox ($189/50 IU), the cost of treatment is relatively high; thus, Prosigne is a financial choice ($51/50 IU). However, BTX-A treatment still has an excellent cost-benefit ratio according to an economic analysis of health [16]. It is understandable that symptom severity was an important factor. Interestingly, patients with depression rather than anxiety preferred BTX-A treatment (Table 2); the reason is unknown, and depression may be related to major blepharospasm severity. Importantly, our study revealed the factors affecting the patients' selections; thus, suggestions for spreading the BTX-A treatment can be explored in future research. Adverse effects were local and mild, including common effects (pain, ptosis, ecchymosis, diplopia, blurred vision, lacrimation, lagophthalmos, and dry eyes) and rare effects (ectropion, hematoma, photophobia, and continuous nasal discharge). In our study, adverse events occurred 52 times (5.0%) with no severe sequelae among 1038 injections, and the majority of adverse effects occurred during the first few treatments, similar to previous reports, suggesting that long-term treatment of blepharospasm with BTX-A is safe.

Interestingly, our study indicates higher dosages and longer response latency with the prolongation of treatment by BTX-A injection, suggesting that long-term treatment of blepharospasm with BTX-A is effective but also fluctuates. It is unknown, however, whether disease progression, either alone or in combination with drug resistance, leads to an efficacy deficit that requires an increased dosage to guarantee an effect [15, 31]. Common reasons that account for low efficacy include underdosing, improper injection technique, presence of eyelid opening apraxia, and resistance. Therefore, proper dosages and techniques can be better applied to dramatically improve the efficacy. Moreover, understanding muscular anatomy is critical to not only ensure optimal results but also reduce adverse effects [32]. Resistance occurs in 5–10% of patients, mostly due to neutralizing antibody production against BTX-A. Several operating regulations should be followed to reduce the risk of antibody production, including low dosages, appropriate intervals (at least 12 weeks), and a rational repeated injection schedule. In our study, low dosages and appropriate intervals were applied. Moreover, the efficacy rate was greater than 90%, and given our vast experience in BTX-A injection techniques, we favor the theory that the chronic, progressive nature of blepharospasm as well as drug resistance leads to an efficacy deficit.

Interestingly, the response latency was longer, and higher dosages were needed to maintain the efficacy over time in our study. Moreover, the efficacy significantly decreased at approximately year 10 after the first injection, raising the question of the appropriate time to start BTX-A treatment if the total efficacy time is limited. Approximately 86.7% of blepharospasm patients in our study were level 3–4 at the initial treatment assessment, indicating that patients may not seek medical help until the symptoms begin to impair their quality of life. Moreover, a long time (approximately 2 years) may be required to obtain an accurate diagnosis. Therefore, early application of BTX-A treatment, once the diagnosis of blepharospasm is established, is beneficial for both patients and their families and may prevent progression of physical and psychiatric symptoms, thus improving the quality of life.

We are aware that our study has several limitations. First, two formulations of BTX-A were administered according to

patient preference, whereas using only one formulation could have led to more accurate efficacy and safety data. However, insisting on a single formulation in actual clinical practice is difficult. To date, Prosigne has not been widely investigated; however, no obvious evidence exists for a significant difference in different formulations in existing research [33], and the 1:1 ratio therefore may be rational. Second, data were collected from medical records, which are subject to availability and accuracy issues due to their retrospective nature. Third, the reliability of the analysis of efficacy beyond 10 years and the estimated prevalence is unclear because few patients have completed more than 10 years of follow-up from our individual clinic. However, our clinic is the best-known and largest clinical center for BTX-A treatment in southern China.

In summary, the onset age was earlier than that in Western countries, and although a higher dosage was needed to maintain reliable long-term efficacy, it seems that beginning BTX-A treatment early is rational, given the long-term safety and efficacy. Moreover, whether BTX-A treatment was selected in clinical practice was somehow dependent on symptom severity and medical expenses. Our study supports the long-term efficacy and safety of BTX-A treatment of blepharospasm and helps to add new knowledge to the field of blepharospasm treatment. However, further studies are still needed.

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Compliance with ethical standards

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

Ethics statement This retrospective study was approved by the institutional ethics committee of The First Affiliated Hospital, Sun Yat-sen University (2018-162). All the patients' consents were obtained. This experiment conforms to the ethics.

Disclaimer The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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