Outcomes of a regional variant of botulinum toxin type A in the treatment of essential blepharospasm and hemifacial spasms: A retrospective study

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Purpose: The aim of this study was to report the outcomes of a regional variant of botulinum toxin type A (BtA) in essential blepharospasm and hemifacial spasm. Methods: The medical records of all patients with facial dystonias, who received at least one dose of BtA between May 2016 and April 2017 were retrospectively evaluated. The pre- and post-injection severity of symptoms, graded using the Jankovic rating system for essential blepharospasm and the Samsung Medical Center grading system for hemifacial spasm, the complications after each sitting, and the mean symptom-free interval were recorded. A correlation analysis was done to identify factors associated with longer symptom-free intervals. A P value < 0.05 was considered statistically significant. Results: The mean age at presentation was 56.62 ± 10.56 years. The mean duration of follow-up was 1.86 ± 2.06 years. The modal disease severity reduced from 5 to 0 in essential blepharospasm and from 2 to 0 in hemifacial spasm a week after injection of botulinum toxin. The mean symptom-free intervals with doses of 20, 22.5, 25, 30, and 50 units were 102.1 ± 44.7, 132.4 ± 35.3, 147.2 ± 61.6, 124.4 ± 55.1, and 142.4 ± 59.7 days, respectively. The commonest complication was lagophthalmos (26.3%; n = 20). Injections for primary dystonias were associated with longer disease-free intervals than those for secondary dystonias (P = 0.02). In nine sittings, the dose was increased for increased severity or presumed resistance, which resulted in a significant increase in the symptom-free interval (P = 0.004) without an increased incidence of complications (P = 0.48). Conclusion: BtA is safe and effective in the treatment of facial dystonias. The drug is more efficacious for primary facial dystonias.

Key words: Blepharospasm, botulinum toxin, facial dystonia, hemifacial spasm

Facial dystonias are involuntary spasms of the facial and/or the neck muscles. They may be idiopathic or secondary to compression or palsy of the facial nerve. A microvascular decompression procedure is useful in compressive dystonias, but there is an inherent risk of permanent nerve damage or stroke.¹ The U.S. Food and Drug Administration has approved the use of botulinum toxin type A (BtA) for the treatment of these disorders, but the effects are temporary.² This retrospective study was devised to report the outcomes of a regional variant of BtA in the treatment of facial dystonias and the factors associated with longer disease-free intervals.

Methods

This was a retrospective, observational study that adhered to the tenets of the Declaration of Helsinki. An ethical committee clearance was obtained before undertaking a review of medical records. Assuming that the risk of minor complications is 5% after use of BtA for facial dystonias, a minimum sample size of 73 injection sittings was required, with 5% precision and 95% confidence interval.³ This sample size was calculated using the statistical formulae provided by Johnston et al.⁴ for retrospective chart reviews.

Patients who had undergone at least one sitting of BtA therapy every year and had undergone a sitting between May 2016 and April 2017 in our eye hospital for a primary or a secondary facial dystonia were included in the study. The following data were retrieved: demographic profile, severity of the disease, details of the intervention(s), progression of symptoms post-intervention(s), and average symptom-free interval. All the medical records were critically evaluated for the completeness of data, and records with missing entries were excluded.

All these cases with suspected facial dystonias were evaluated in the following manner before planning for a BtA injection. A detailed history was obtained to rule out a psychiatric disorder that could be responsible for dystonic movements. A detailed drug history was recorded in all cases to rule out a possible drug-induced acute or tardive dyskinesia and to exclude the risk of increased complications and their associated longer disease-free intervals.

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synergistic effect with BtA. All patients underwent a slit-lamp evaluation to screen for local factors responsible for secondary blepharospasms such as blepharitis, trichiasis, entropion, foreign body, epithelial defect, and ocular surface/intraocular inflammation. A systemic evaluation was conducted to rule out an underlying neurological ailment. Evaluation of all the cranial nerves was done to rule out a secondary dystonia. A magnetic resonance imaging was ordered in all cases of hemifacial spasm to rule out an underlying facial nerve compression. At 7 days postintervention, the patients were evaluated for the development of facial asymmetry, lagophthalmos, ectropion, ptosis, corneal punctate erosions, and the persistence of symptoms. Schirmer’s test was done if the patient had symptoms suggestive of a dry eye disorder.

The severity of blepharospasm was graded using the Jankovic Rating Scale (JRS).[5] The JRS is divided into two sections with five grades in each part. The first section grades the severity of blepharospasm as follows: 0 – no blinking; 1 – increased blinking only on external stimuli; 2 – mild, but spontaneous, definitely noticeable blinking; 3 – moderate and mildly incapacitating symptoms; and 4 – severe and incapacitating symptoms. The second section scores the frequency of blepharospasm as follows: 0 – no increased blink frequency; 1 – mildly increased blink frequency; 2 – eyelid fluttering lasting for less than 1 second duration; 3 – spasms lasting for more than 1 second, but the eyes are open more than 50% of waking hours; and 4 – functionally blind due to persistent spasm for more than 50% of the waking hours. In our study, the sum of the scores for the two parts was considered as the final grade.

The Samsung Medical Center grading system (SMC), which is a 4-point system, was used for grading hemifacial spasm.[6] The grades in the system are as follows: 1 – localized spasm of the periorcular area; 2 – involuntary movements spreading to other parts of the ipsilateral face; 3 – interference with vision due to frequent tonic spasms; and 4 – disfiguring asymmetry with continuous contraction of the muscles.

All interventions were performed by a single surgeon. BotoGenie® (Bio-Med Private Limited, Ghaziabad, Uttar Pradesh, India), a lyophilized powder with a strength of 50 IU, freshly reconstituted with 2 mL of pyrogen-free, sterile normal saline (concentration = 2.5 IU/0.1 mL) was used for chemodenervation in all cases. At each injection site, 2.5 to 5 IU aliquots of BtA were injected. In case of blepharospasm, injections were administered to the medial and lateral pretarsal orbicularis oculi of the upper and the lower lids. The procerus and the corrugator supercilia were also injected in select cases. The dose was varied according to the preinjection severity and the resistance to therapy. For hemifacial spasm, the injections were given in eight to 10 sites, depending on the extent of involvement and the severity of the disease. The improvement of symptoms and complications were recorded on the first follow-up visit (7 days post-intervention) in each case.

Continuous variables were summarized as mean and standard deviation. Categorical variables were either summarized as frequency and percentage or mode. Student’s t test (two-tailed) and \( \chi^2 \) tests were used to compare the mean difference between the two groups. The effect of the drug in the two groups and genders was compared by the one-way analysis of variance (ANOVA) test. The correlation between the dose and the efficacy of the drug was determined by the Spearman’s rank coefficient. A \( P \) value < 0.05 was considered statistically significant.

**Results**

A total of 26 patients met the inclusion criteria, out of which three patients had blepharospasm and 23 had hemifacial spasm. None of the medical records had to be discarded for missing entries. Seven patients had an underlying vascular loop syndrome. Table 1 summarizes the demographic characteristics of our study participants.

A total of 76 sittings of BtA therapy were included in our study. Fig. 1 shows the pre- and post-intervention photographs from one of our study participants. Table 2 is the frequency distribution table that clusters the patients according to the number of sittings. There was a statistically significant increase in the symptom-free interval with a larger number of sittings (\( f \)-ratio value = 3.87, \( P = 0.026 \)). Most of the sittings involved a total dose of 25 IU (\( n = 51 \); 67.1%). The average disease-free interval was 139.92 ± 58.53 days. Fig. 2 shows the average symptom-free interval with each dose.

A correlation analysis was conducted to identify the factors that were associated with longer disease-free intervals, suggestive of a better efficacy. Neither the gender of the patient nor the duration of symptoms at first presentation affected the length of the disease-free interval (\( P = 0.84 \) and 0.32, respectively). Overall, there was no statistically significant correlation between the total dose administered in a sitting and the symptom-free interval (\( \rho = -0.12; \ P = 0.31 \)). However, significantly longer disease-free intervals were noted in primary dystonias (135.11 ± 54.15 days) than in secondary dystonias (75.29 ± 48.89 days) as shown by the one-way ANOVA test (\( f \)-ratio value = 6.46; \( P = 0.02 \)). Moreover, in nine sittings, a decision to administer an increased dose of BtA was undertaken. Table 3 summarizes the effect of the increased dose on the symptom-free interval. There was a statistically significant increase in the duration of the symptom-free interval with the incremented dose (\( f \)-ratio value = 15.49; \( P = 0.004 \)). However, with the increased dose, two patients developed lagophthalmos: one developed ptosis and the other developed deviation of the angle of the mouth.

There was a statistically significant increase in the disease-free interval with subsequent injections at doses of 22.5 IU per sitting (\( \rho = 0.66; \ P = 0.04 \)). But doses of 20, 25, 30, and 50 IU were not associated with a similar increase in efficacy with subsequent injections (\( P = 0.59, 0.26, 0.87, \) and 0.37, respectively).

The overall complication profile of the drug was the same for both primary and secondary dystonias. The complication rate for primary dystonias was 33.3% (\( n = 23 \)) and that for secondary dystonias was 42.9% (\( n = 3 \)). There was no systemic, life-threatening, or vision-threatening complication in either group. Table 4 shows the distribution of complications in the two groups.

The participants who developed lagophthalmos after the injection were treated with ocular lubricants and lid taping at bedtime. The lagophthalmos disappeared spontaneously, usually within 3 to 5 weeks. None of the other complications encountered in our study needed treatment.
Table 1: Demographics of our study participants

| Parameter                        | Primary facial dystonia | Secondary facial dystonia | Overall      | $P$  |
|----------------------------------|-------------------------|---------------------------|--------------|------|
| Age (years)*                     | 56.89±11.32             | 55.86±9.90                | 56.62±10.56  | 0.83†|
| Gender†                          |                         |                           |              |      |
| Male                             | 10 (52.6)               | 4 (57.1)                  | 14 (53.8)    | 0.84‡|
| Female                           | 9 (47.4)                | 3 (42.9)                  | 12 (46.2)    |      |
| Phenotype‡                       |                         |                           |              |      |
| Blepharospasm                    | 2 (20)                  | 1 (14.3)                  | 3 (11.5)     | 0.79‡|
| HFS                              | 17 (80)                 | 6 (85.7)                  | 23 (88.5)    |      |
| Laterality (HFS)†                |                         |                           |              |      |
| Right                            | 8 (47.1)                | 2 (33.3)                  | 10 (43.5)    | 0.56§|
| Left                             | 9 (52.9)                | 4 (66.7)                  | 13 (56.5)    |      |
| Duration of illness at presentation (years)* | 2.73±2.71              | 4.03±5.08                 | 3.15±3.46    | 0.32‡|
| Severity at presentation§        |                         |                           |              |      |
| Blepharospasm                    | 4                       | 6                         | 4            |      |
| HFS**                            |                         |                           |              |      |

*Expressed in terms of mean±standard deviation; †Two-tailed Student's $t$-test; ‡Expressed in terms of frequency (percentage); §$\chi^2$ test; ‡Summarized in terms of mode; °Severity graded by Jankovic Rating Scale; **Severity graded by Samsung Medical Center grading system; HFS=hemifacial spasm

Table 2: Number of sittings per participant

| Number of sittings | Frequency | Disease-free interval (days)* |
|--------------------|-----------|------------------------------|
| 1-3                | 18        | 111.17±59.73                 |
| 4-6                | 4         | 148.71±74.81                 |
| 7-9                | 4         | 152.68±42.16                 |

*Summarized as mean±standard deviation

Discussion

There are several methods of treating facial dystonias. Tight bands across the forehead, tight glasses, glasses with a palpebral splint, and dark goggles are nonpharmacological ways of treating blepharospasm that may provide only temporary relief. [7] Oral benzodiazepines, GABA (gamma-aminobutyric acid)-B blockers, and dopamine-modulating therapies may be helpful, but they alter the cognitive function and induce somnolence. [7] Microsurgical decompression produces lasting results in vascular loop syndromes, but there is a high risk of permanent neurodeficit or stroke. [11] Alcohol or anesthetic substances may be injected intramuscularly, but the effect fades out too rapidly to be clinically useful. Breinin et al. [9] and Jacoby et al. [9] found that cadmium and diltiazem reduced muscle contractility in vivo and in vitro, but their results were never put to clinical tests. Antibiotics such as doxorubicin may also be used as an alternative therapy that can theoretically induce a permanent cure. [10] But the drug induces a localized necrosis, causes destruction of the injected muscle, and results in a cutaneous reaction.

The most popular mode of treating facial dystonias is with injections of BtA. However, a meta-analysis has concluded that there is only Level B evidence for the use of BtA in blepharospasm and Level C evidence for its use in hemifacial spasms. [11] This apparent disparity between popular belief and the conclusions of this evidence-based review is mainly because of a lack of large, well-designed randomized trials.

A major difficulty in the interpretation of studies using BtA is the presence of a large number of different commercially available preparations (e.g., onabotulinumtoxin A, abobotulinumtoxin A, incobotulinumtoxin A, etc.). [13] One unit of a given preparation is specific and is not comparable to one unit of any other preparation because of the differences in the vehicle dilution schemes, the laboratory protocols, and the differences in species sensitivities. [13] Therefore, the results of any study can only reflect the specific variant of BtA that is used and cannot be extrapolated to all the different preparations available in the market. Moreover, a large number of regional variants of BtA are now available in the market, but data regarding their efficacy, dosage schedules, and complication profiles are difficult to find in contemporary literature. [14] In this study, the results of treatment of facial dystonias with a regional variant of BtA have been reported.

We included 26 patients who had a total of 76 sittings of BtA injection for facial dystonias. The patients were divided into those with primary and secondary dystonias. The two groups were comparable with regard to their demographic profiles. Five different doses were used depending on the severity of the disease. The mean symptom-free interval postinjection in our study varied from 3.4 to 4.9 months (102.1–147.2 days) with different doses of the drug. This is comparable with the reports of Wang et al. [1] and is slightly greater than that reported by Anwar and Zafar. [13]

The patients were clustered into three groups based on the number of sittings of BtA injections received. When these groups were compared, a steady increase in the mean symptom-free interval was noted with a greater number of sittings ($P = 0.026$). This corresponds to the observations of Oyama et al. [18] as well. A literature search revealed that the most important cause for this effect is a disuse atrophy of the facial musculature secondary to repeated BtA injection. [17]

Similar to contemporary literature, we could find no relationship between the symptom-free interval and the age or gender of the study participant ($P = 0.84$ and 0.32, respectively). [18] However, at 22.5 IU/sitting, there was a statistically significant increase in the efficacy with each subsequent dose ($P = 0.04$). This result is probably due to a Berksonian bias. The dose of the injection was chosen according to the severity of the spasm at every visit, and we switched over to a higher dose whenever the spasms were
resistant. As a result, patients receiving lower doses of the drug actually had a less-resistant disease and were likely to be symptom-free for a longer period of time. A similar result should have been achieved with a dose of 20 IU/sitting, but there were very few sittings where this dose was used (n = 4; 5.3%), and so it could not achieve a statistical significance (P = 0.59). This corresponds to the observations of Anwar and Zafar,\textsuperscript{15} who noted that 23.52% of the study participants felt almost cured after three to five injections of BtA and stopped the treatment. In the rest of the patients, who were more resistant to therapy, the dose of the drug had to be increased, and they required regular injections for prolonged periods.\textsuperscript{15}

Table 3: Effect of increment in dose on the symptom-free interval

| Initial dose (units) | Symptom-free interval\textsuperscript{1} | New dose (units) | Symptom-free interval\textsuperscript{1} | Increment in dose (units) | n\textsuperscript{*} |
|----------------------|----------------------------------------|------------------|----------------------------------------|---------------------------|-----------------|
| 20                   | 92.67±20.55\textsuperscript{i}         | 25               | 155.67±42.36\textsuperscript{i}        | 5                         | 3               |
| 22.5                 | 166.5±20.51\textsuperscript{i}         | 25               | 184.5±12.02\textsuperscript{i}        | 2.5                       | 2               |
| 22.5                 | 80                                     | 50               | 227                                    | 27.5                      | 1               |
| 25                   | 68                                     | 30               | 116                                    | 5                         | 1               |
| 25                   | 30.5±12.02\textsuperscript{i}         | 50               | 95.5±51.62\textsuperscript{i}         | 25                        | 2               |

\textsuperscript{1}Frequency; \textsuperscript{1}Expressed in days; \textsuperscript{i}Expressed as mean±standard deviation

Table 4: Complication profile of the two groups

| Parameter                        | Primary facial dystonia\textsuperscript{*} | Secondary facial dystonia\textsuperscript{*} | P\textsuperscript{†} |
|----------------------------------|---------------------------------------------|-----------------------------------------------|-----------------------|
| Lagophthalmos                    | 18 (26.1)                                    | 2 (28.6)                                      | 0.8                   |
| Deviation of angle of mouth      | 2 (2.9)                                      | 1 (14.3)                                      |                       |
| Ptosis                           | 2 (2.9)                                      | 0 (0)                                         |                       |
| Persistent twitching             | 1 (1.5)                                      | 0 (0)                                         |                       |
| Total                            | 23 (33.3)                                    | 3 (42.9)                                      |                       |

\textsuperscript{*}Summarized as frequency (percentage); \textsuperscript{†}Two-tailed t-test

Figure 1: (a) Preinjection photograph of one of our study participants with right-sided hemifacial spasm. (b) One week postinjection of 25 units of botulinum toxin type A in the same patient showing cessation of symptoms.

In nine sittings, the total dose of BtA administered was increased in view of severity or presumed resistance. There was a statistically significant increase in the symptom-free interval with the increased dose (P = 0.004). This corresponds to the observations of Frueh and Musch\textsuperscript{19} and Scott et al.\textsuperscript{20} Moreover, there was no significant difference in the incidence of complications with the incremented dose (P = 0.48). This can be explained by the fact that the maximum dose received per sitting in this study was only 50 units. In published literature, it has been shown that only when the mean dose per eyelid exceeds 25 units or more, the incidence of side effects increases disproportionately compared to the increase in the symptom-free interval.\textsuperscript{19}

Participants with primary dystonias experienced longer disease-free intervals than those with secondary dystonias after the first injection of BtA. This corroborates with the findings

Figure 2: Point plot showing the mean symptom-free interval after different doses of botulinum toxin
of other contemporary investigators. It is believed that secondary facial dystonias produced by vascular compression syndromes are more resistant to chemodenervation tactics because of the inherently strong compression forces at play.

In our study, the commonest complication with this intervention was lagophthalmos, followed by deviation of the angle of the mouth and ptosis. But none of these complications required a major intervention. The occurrence of complications following an injection of BtA for a facial dystonia is rare. The incidence of ptosis following BtA injection has been reported in 5.88% to 22% of cases in literature. Exaggerated symptoms of dry eye and features of facial weakness have also been reported. One study has also shown an improvement in the features of dry eye post-injection. This difference in the complication profile in different reports is probably due to different dosage schedules and/or slightly different techniques of administration.

This study suffers from the inherent weaknesses of a retrospective study design. A recall bias about the symptom-free interval could not be ruled out. There was an unequal distribution of patients with blepharospasm and hemifacial spasm. A larger sample with a more equitable distribution between blepharospasm and hemifacial spasms would have helped us identify specific factors that are associated with better efficacy of BtA in each group.

**Conclusion**

This study provides data regarding outcomes of a regional variant of BtA in the treatment of facial dystonias. This study shows that BtA provides temporary but significant relief for symptomatic patients with primary and secondary facial dystonias. It also shows that increasing the dose of BtA in resistant or severe cases improves the symptom-free interval.

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**Conflicts of interest**

There are no conflicts of interest.

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