Botulinum toxin-A injection in esotropic Duane syndrome patients up to 2 years of age

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PURPOSE To evaluate the role of botulinum toxin-A (BTX) injection as the primary treatment for patients with esotropic Duane retraction syndrome ≤2 years of age.

METHODS The medical records of patients with esotropic Duane syndrome who underwent unilateral or bilateral BTX injection to the medial rectus muscle at or before 2 years of age were reviewed retrospectively. The following data were extracted from the record: laterality, age at the time of injection, primary position deviation, duction deficit, anomalous head posture, globe retraction before and after injection, further surgeries, and complications. Success was defined as permanent resolution of esotropia and head turn in primary position at final follow-up.

RESULTS A total of 15 patients (14 unilateral, 1 bilateral) were included. Before BTX injection the mean primary esotropia at near with full cycloplegic refraction was $29.3^{\Delta} \pm 14.4^{\Delta}$; the mean head turn, $23^{\circ} \pm 11^{\circ}$. Mean duration of follow-up was 37 ± 29 months (range, 7-96 months). Orthotropia and resolution of head turn was achieved in 7 patients (46.7%). In subgroup analysis, success rate gradually decreased from 100% in patients ≤7 months of age to 33.3% in patients 8-12 months of age, and 20% in patients >12 months of age. Seven patients (46.7%) required surgery (medial rectus recession and/or superior rectus transposition) because of residual head turn and esodeviation following BTX.

CONCLUSIONS In this patient cohort, orthotropia in primary position and correction of head turn were achieved with a single BTX injection in about half of the patients ≤2 years of age and all patients ≤7 months of age. BTX injection early in infancy can obviate the need for surgery in esotropic Duane syndrome. (J AAPOS 2019;23:25.e1–4)

Duane retraction syndrome, the most common congenital cranial dysinnervation disorder, is characterized by limitation of horizontal eye movements, globe retraction and changes in the palpebral fissure.[1] In its most common form—esotropic Duane syndrome—patients present with esotropia, limited abduction, and a compensatory head turn to the affected side. Significant esodeviation in primary position and noticeable head turn constitute the major indications for surgery in esotropic Duane syndrome and can be addressed with several surgical procedures, including unilateral/bilateral medial rectus recession, vertical rectus transposition, superior rectus transposition, or inferior rectus transposition.[2-5]

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Botulinum toxin-A (BTX) treatment is widely accepted as an alternative to surgery in select types of strabismus, such as residual or consecutive deviations after surgery, acute paralytic strabismus, acute thyroid orbitopathy, cyclic esotropia, and acute esotropia.[6-8] However, few studies have evaluated its role in the treatment of Duane syndrome, and these studies are limited by their short follow-up, heterogeneous patient population, and ill-defined results.[9-11] The purpose of this study was to evaluate the efficacy of BTX injection in patients with esotropic Duane syndrome ≤2 years of age.

Subjects and Methods

The medical records of children diagnosed with esotropic Duane syndrome who underwent single BTX injection into the medial rectus muscle to correct esodeviation and head turn at or before 2 years of age were retrospectively reviewed. All patients were treated by a single ophthalmologist (ECS) in private practice. Those with a minimum follow-up of 6 months were included. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Ankara Numune Training and Research Hospital Institutional Review Board.

All patients underwent complete orthoptic and ophthalmological assessment by a single ophthalmologist (ECS) before and

Table 1. The clinical characteristics of patients with esotropic Duane syndrome before and after botulinum toxin-A injection

				Primary deviation		Head turn		Adduction		Abduction		Globe retraction	
Case	Laterality	Age at BTX, months	Follow−up, months	Before BTX	After BTX[a]	Before BTX	After BTX[a]	Before BTX	After BTX[a]	Before BTX	After BTX[a]	Before BTX	After BTX[a]
1	Right	5	68	15	0	10	0	0	0	−4	−3	+2	+1
2	Left	5	36	40	0	15	0	0	−0.5	−4	−4	+3	+2.5
3	Right	6	24	30	0	25	0	0	−0.5	−4	−2	+2.5	+1.5
4	Bilateral	7	18	35	0	0	0	0	−1	−4	−1	+3	+4
								0	0	−5	−2	+3	+3
5	Right	8	72	30	0	30	0	0	0	−5	−1		
6	Left	8	12	30	0	20	−10	0	0	−4	−4		
7	Left	8	48	40	40	40	40	0	0	−4	−3	+1	+1
8	Right	9	24	30	20	40	20	0	0	−4	−4		
9	Right	11	24	25	25	20	20	0	0	−4	−4	+3	+3.5
10	Right	12	8	10	10	15	10	0	0	−3.5	−3.5	+1.5	+1.5
11	Right	14	80	10	0	25	0	0	−1.5	−4	−4	+3	+1
12	Left	18	8	15	30	30	30	0	0	−3.5	−4	+0.5	+0.5
13	Left	18	30	20	20	15	20	0	0	−2.5	−3	+0.5	+1.5
14	Left	24	96	50	14	30	10	0	0	−5	−3		
15	Right	24	7	60	40	30	30	0	0	−5	−5		

BTX, Botulinum toxin-A.
[a]After BTX measurements at the final follow−up or at last visit before a surgery (for patients who required surgery after BTX injection).

after BTX injection. Full cycloplegic correction was provided to patients with hyperopia of >1.50 D (spherical equivalent) or astigmatism of at least 2.5 D. The data collected from the patients' records included laterality, age at the time of BTX injection, primary deviation at the primary position, duction deficit, anomalous head posture and globe retraction before and after BTX injection, further surgeries, and complications. Primary deviation was measured in the primary position with alternate prism cover testing (prism held at the affected eye), with appropriate correction in place, at near and distance. The Krimsky test was used in uncooperative cases. The degree of head turn was determined using a goniometer in cooperative patients as an estimate of angle between the line of vision and the direction of nose while the patient was viewing a cartoon or a 20/32 target at distance. Ocular ductions were recorded in nine positions of gaze on a scale of 0 to −5, with 0 indicating full motion and −5 indicating unable to reach the midline). Ocular alignment measurements at the last follow-up or before any surgery (for patients who required further surgery after BTX injection) were used to report postoperative outcomes.

BTX injection was performed by the same surgeon (ECS) under general anesthesia. Medial rectus insertion was grasped and the globe was abducted using toothed forceps, and a mean dosage of 2.5 IU of BTX diluted in 0.1 mL of saline was injected into the ipsilateral medial rectus muscle, without a conjunctival incision, under a surgical microscope. Patients were examined 2-4 weeks after injection to confirm that the BTX was having an effect. Success was defined as permanent resolution of esotropia and head turn in primary position at final follow-up after single BTX injection.

Statistical analysis was performed using SPSS Statistics ver. 17.0 (SPSS Inc, Chicago, IL). Wilcoxon signed-rank test was used to analyze the findings on head turn and esotropia before BTX injection and at last follow-up. A P value of <0.05 was considered statistically significant.

Results

A total of 15 children (8 girls) who met inclusion criteria were identified. One child had bilateral Duane syndrome and received bilateral BTX injection. The rest of the children received BTX injection to the ipsilateral medial rectus muscle. The mean age at BTX injection was 11.8 ± 6.4 months (range, 5-24).

The mean esodeviation at primary position was $29.3^{\Delta} \pm 14.4^{\Delta}$ (range, 10^{Δ}-60^{Δ}), and mean head turn was 23° ± 11° (range, 0°-40°) before BTX injection. Limitation of abduction was present in all patients and ranged from −5 to −2.

The mean esotropia significantly improved to $13.3^{\Delta} \pm 15.1^{\Delta}$ (range, 0^{Δ}-40^{Δ}; $P = 0.009$), and head turn improved to 11° ± 15° (range, −10° to 40°; $P = 0.008$) at last follow-up (an average of 37 ± 29 months after injection). Complete success, with resolution of primary esodeviation and head turn, was observed in 7 patients (47%; Table 1). One patient had partial improvement, leaving a primary esodeviation of 14^{Δ} and head turn of 10° at 8 years' follow-up. Seven patients required follow-up surgery because of residual esotropia of $26.4^{\Delta} \pm 11.1^{\Delta}$ (range, 10^{Δ}-40^{Δ}) and head turn of 24.3° ± 9.8° (range, 10°-40°). The study group was further divided into subgroups by patient age. This subgroup analysis revealed that the success rate of BTX injection was 100% in children treated at ≤7 months of age, 33% in children treated between 8-12 months of age, and 20% in children treated after 12 months of age. Figure 1 shows the ocular motility pattern in case 4 before and after BTX injection.

Three patients developed mild ptosis that resolved within 3 months of BTX injection. No patient suffered from pupillary occlusion because of induced ptosis. Limitation of adduction was documented in 4 patients (cases 2, 3, 4, and 11) with successful outcome, ranging between −0.5 and −1.5.

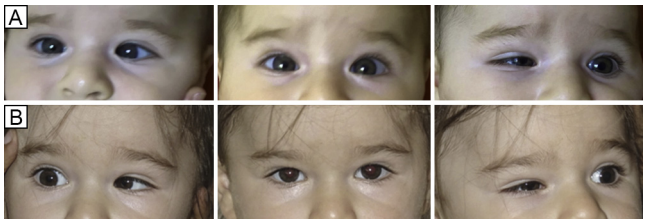

FIG 1. A patient with bilateral esotropic Duane syndrome. A, Before botulinum toxin-A injection. B, 1.5 years after injection to both medial rectus muscles.

Discussion

Significant esodeviation in the primary position and head turn are the major indications for treatment of esotropic Duane syndrome. They can be addressed with several surgical procedures, including unilateral or bilateral medial rectus recession, vertical rectus transposition, superior rectus transposition, or inferior rectus transposition.[2-5] In most of the published studies,[2,3,12,13] the mean age at surgery ranges between 9.3 and 13 years, both because the symptoms are usually less prominent at younger ages[14] and because signs of aberrant innervation and motility pattern can also be difficult to assess in full detail in very young patients. Therefore, surgery is generally delayed until the age that allows precise and thorough orthoptic evaluation. However, some patients presenting with significant esotropia and head turn in infancy require an intervention at an earlier age. We felt that BTX injection could be a promising alternative to surgery in children presenting with marked esotropia and head turn at or before 2 years of age in whom exact orthoptic measurement and precise surgical planning cannot be performed.

Data regarding the long-term outcome of BTX injection in esotropic Duane syndrome, particularly in younger patients, is limited.[9-11,15] Talebnejad and colleagues[9] reported 3 patients with type 1 Duane syndrome treated with BTX injections; 2 of the 3 were orthotropic at 6 months' follow-up; however, these patients were already orthotropic or had esotropia of $<10^{\Delta}$ of esotropia before BTX injection. Dawson and colleagues[15] investigated the role of BTX as a diagnostic tool to identify Duane syndrome patients that might benefit from further surgery. The angle of deviation was reduced in 53% of their patients in the long term; however, this study involved a mixed group of patients with Duane syndrome, and the clinical characteristics of patients, the follow-up period, and the success rate after injection were not clear. Recently, Ameri and colleagues[11] studied the efficacy of BTX injection in 16 patients with type 1 Duane syndrome with an age range of 1-21 years and reported complete success (residual deviation of $<8^{\Delta}$ and residual head turn $<5°$) in 37.5%. The detailed clinical characteristics of successful cases were not provided, and the follow-up time was relatively short compared to our study. In the study by Ameri and colleagues,[11] the successful outcome was related to the amount of restriction on forced ductions. Unfortunately, we do not have the complete data on forced duction test results during injection in our cases to be able to test this finding.

In our study cohort, orthotropia was achieved in 7 of 15 patients, and no further surgery was required in 8 patients after a single injection to the medial rectus muscle on the affected side. Our success rate was 100% in patients $\leq$7 months of age and decreased with increasing age. Children older than 14 months of age received no clinical benefit (Table 1). Previously, Maya and colleagues[10] reported success (0^{Δ}-4^{Δ} of esotropia) in half of their 8 patients, up to 3 years of age, after bilateral BTX injections with esotropic Duane syndrome. From the data derived from their tables, the successful cases in this study were at 10, 12, 28, and 31 months of age at the time of injection, achieving a success rate of 100% for 2 children $\leq$1 year of age and 33.3% for children 1-3 years of age.

The therapeutic effect of BTX in strabismus involves two phases. The acute effect of BTX treatment gradually wears off in approximately 3 months and results from the paralysis of the injected muscle due to the presynaptic blockage of cholinergic transmission. The resultant changes in the length-tension curve of the injected muscle and its antagonist and the remodeling of myofibers are responsible for the long-term improvement in ocular alignment.[6] Studies on infantile esotropia have shown that this permanent effect is much more striking in younger patients, achieving a satisfactory alignment in all patients treated at or before 7 months of age.[16]

The major advantage of botulinum toxin injection over surgery is the shorter duration of treatment and reduced anesthesia time.[8] This is especially important for the age group in our study, because several studies have shown that prolonged anesthesia could affect brain development and result in learning disabilities in younger children.[17] A second advantage of BTX is the preservation of muscles and ciliary circulation for future surgery. Finally, with BTX, surgeons can offer early treatment despite lack of a thorough orthoptic evaluation.

The complications encountered in our study population were mild ptosis (20%), which resolved within 3 months of injection, and limitation of adduction (26.7%). Although we did not encounter them, other potential complications after BTX injections include severe ptosis leading to amblyopia, subconjunctival hemorrhage, vertical deviation, and disrupted binocularity due to prolonged overcorrection.

Our study results are limited by the small patient population and the absence of a control group. Despite these limitations, our results are still encouraging and suggest that chemodenervation with BTX may obviate the need for strabismus surgery in some children with Duane syndrome, if applied before 8 months of age. Further studies with larger sample sizes and different age groups are required to confirm our results.

Literature Search

The authors searched PubMed on April 4, 2018, for English-language results using the following terms: *botulinum toxin*, *chemodenervation*, and *Duane syndrome*.

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