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The role of botulinum toxin in management of infantile esotropia

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Abstract

Purpose: To find out the effect of a single dose botulinum toxin injection.

Methods: This study is an observational case series. Data of patients with infantile esotropia who received a single dose of botulinum toxin in 6th-9th month of their age were retrospectively reviewed during the period from February 2013 to January 2015. Botulinum toxin was injected in each of medial recti with a dose of 5 IU/0,05 mL without Electromyography (EMG) control. Five patients were included in the study. Complications reletad to injection and to the toxin were recorded. During their regular follow-ups, the parents were instructed to patch the dominant eye if there is fixation preference either in exotropia or esotropia phases. Patients were examined between their 72nd to 96th month to find out their current visual acuity and to observe if they had any late term accompanying squints, nystagmus and amblyopia. Snellen optotypes or pictures were used for detecting best-corrected visual acuity.

Results: Orthophoria was the main outcome for 3 of the 5 patients. Dissociated deviations and latent nystagmus did not develop on any patient. On the last examination, patients' visual acuities were assesed.

Orthophoric ones: One patient had 1.0/1.0 visual acuity, one patient had 0.4/0.6 visual acuity, one patient had 0.2/0.2 visual acuity.

Monocular esotropia ones: On the strabismic eye 0.1, on the dominant eye 1.0 visual acuity was detected. Inferior oblique muscle hyperfunction developed post injection on all the patients.

Conclusions: Botulinum toxin injection caused infantile esotropia to change into a more manageble form.

Keywords: Infantile esotropia; Botulinum toxin; Chance of visual maturity.

Introduction

Infantile esotropia is a constant esotropia type that occurs before the first year of life. But generally its onset is before the first 6 months of life. Meanwhile, the misalignment that occurs for one out of three infants around the age of 2-4 months is transient esotropia [1].

The exact cause of infantile esotropia still remains unknown. The majority accept that it is a primary dysfunction in the normal development of binocular sensitivity and think that there is a congenital defect in the infant's visual system. According to this thought, it is an innate and constant fusional defect. So surgery can be deferred and done mostly for cosmetic purposes [2-4]. On the other hand, some authors [2] presume that the neural components necessary for normal binocular vision are present at birth, and they suggest that poor fusion and lack of high-grade stereopsis is probably a sensory adaptation caused by the motor misalignment. Thus, surgical correction should

be performed early during infancy [2,5]. But the early surgery opinion has an objection within itself: Von Noorden defends that examination of infants between 6 to 12 months most likely will be inadequate. Most probably, measurements of the preoperative deviation will be unable to be done exactly. Therefore surgery based on inadequate information would end up with a high number of overcorrections and undercorrections. And the result, thereby, detracts from the original purpose [6].

So, it remains uncertain when surgery should be performed in order to obtain the best long-term results. In this perspective, can an intervention of botulinum toxin injection give a chance to re-assess the consequences of infantile esotropia whether it is associated with congenital defect in the infant's visual system or with a sensory adaptation caused by the motor misalignment? also, can botulinum toxin injection give a chance to defer the surgery, if it is a sensory adaptation? thereby, can overcorrection or undercorrection be avoided?.

In this study we retrospectively reviewed the results of the patients who underwent botulinum toxin injection between 6 to 9 months of age and who have not received any more intervention up to their last follow-up. By this way, the strabismus surgery was deferred and also, the patients had a chance of becoming ortophoric in a part of their childhood stage. So, in this study an analysis can be done between the two standpoints about time of correction in infantile esotropia.

Materials and methods

This single-center study was carried out in a tertiary health facility. It is a retrospective review of data on consecutive patients. The patients whose injections were done by the same surgeon were included. The injections were conducted during the period from February 2013 to January 2015 and the patients who had a follow-up in their 6th-8th year were included. The Institutional Ethics Committee approval was obtained under number of 924 at the date of 11/05/2021. The tenets of the Declaration of Helsinki were followed. Consent from the parents was obtained for use of figures accompanying this paper. Children who have developmental delay or preexisting neurological disorders were excluded. Children who did not have a follow-up at least for one month of post-injection, and had a concomitant eye disease such as congenital cataract or its surgery before and after injection were excluded. Patients who have strabismus surgery up to their last follow-up were excluded, too.

Pre-injection ophthalmological examinations included evaluation of hirschberg corneal reflex test, doll's eyes reflex test, the presence of fixation preference, cycloplegic refraction with cyclopentolate hydrochloride 1.0%, fundus inspection, and ocular motility. Ocular motility examination included inspection of Dissociated Vertical Deviation (DVD), İnferior Oblique Muscle Hyperfunction (IOHF), and nystagmus. Patients with a refractive error were assisted with eyeglass wearing and if there was no change in their esotropic angle by eyeglass wearing they were classified as infantile esotropia.

Main outcome measures are orthophoria development, visual acuity of the patients in their 6th-8th year, and the rate of DVD, IOHF, and nystagmus. A 50 units Botulinum Toxin type A containing vial (BotoxTM Allergan) was diluted with 0,5 mL BSS (balanced salt solution), and prepared in a concentration of 5 IU/0,05 mL. The toxin was put in an insulin syringe. A 0,05 mL dilution containing 5 IU botulinum toxin were injected in each of medial recti without Electromyography (EMG) control. The injections were done under general anestasia. The medial rectus muscle belly was grasped via an adson forceps. Then, the toxin was injected to the rectus through closed conjunctiva beyond the grasped area via a 27 gauge needle.

Five patients were included in the study. Following the injection, one patient was examined regularly until 88th month, one 26th month, two 9th month, one 3rd month post-injection, in addition of the examinations between 72nd and 96th months.

Complications related to injection and to toxin were recorded. During their regular follow-ups and preinjection examinations, the parents were instructed to patch the dominant eye if there is a fixation preference either in exotropia or esotropia phases. When the patients were examined between their 72nd and 96th months, their current visual acuity, status of orthophoria and late term accompanying squints, nystagmus and amblyopia were assesed. Best-corrected visual acuity was detected with snellen optotypes or pictures.

Each patient is separately described. So statistical analysis was not required.

Results

Nine patients underwent botulinum toxin injection between February 2013 to January 2015. Four patients were excluded from the study. One patient was found to have a congenital cataract surgery before the injection. For one patient, it was found he had undergone strabismus surgery late after. And for two patients, it was found they had follow-up records shorter than one month. So, five patients were included in the study.

Based on post injection interim observations derived from the follow-ups: At first, a temporary orthophoria developed between the 1st and 2nd weeks (5 patients) but then a temporary exotropia developed between the 2nd and 4th weeks (5 patients). Again, orthophoria developed between the 1st and 3rd-4th months (5 patients).

At their last examination (between 72nd and 96th month) on the horizontal plan, orthophoria on 2 patients, monocular esotropia on 2 patients and alternan esotropia with a high accommodative convergence component that can be corrected partially by eyeglass on one patient were detected. Patients' visual acuities were assesed, too. Orthophoric ones who had IOHF development in 88th month of his age had 1.0/1.0 visual acuity (Figure 1), in 16th month of her age had 0.4/0.6 visual acuity (Figure 2), and in 13th month of her age had 0.2/0.2 visual acuity (Figure 3). In this state, there seems to be an inverse proportion between visual acuity and IOHF development age. Monocular esotropia ones: On the strabismic eye 0.1, on the dominant eye 1.0 visual acuity was detected (Figures 4 and 5). These patients were not compliant on their follow-ups so exactly when IOHF development happened was not determined but IOHF developed post injection on all the patients in the 13th month age at the earliest and in the 88th month age at the latest.

Dissociated deviations and latent nystagmus did not develop on any patient. These -as known- occur as a result of visual immaturity, and they are expected complications in infantile esotropia. Absense of them is the most important unexpected findings of this observation.

Table 1: Table of all the infants with key clinical details over time. Unit of time and age are set to month.

Cases	1	2	3	4	5
Age of injection	8	7	6	6	9
Refraction at the age of injection	+0.5D/+0.5D	+4.5D/+4.5D	emetropia	+3.25 +1.25x90 D/4.25 +1.25x35 D	+2.5D/+2.5D
Regular follow-up to	88	9	26	3	9
Age of IOHF development	88	16	13	unknown	unknown
Age at the last examination	96	81	81	78	72
Visual acuity at the last examination	1.0/1.0	0.4/0.6	0.2/0.2	0.1/1.0	1.0/0.1
Status of squint at the last examination	ortophoria	Alternan esotropia	ortophoria	esotropia	esotropia
Dissociated deviation at the last examination	none	none	none	none	none
Latent nystagmus at the last examination	none	none	none	none	none
Time of becoming ortophoric post injection	3-4	7	3	none	none

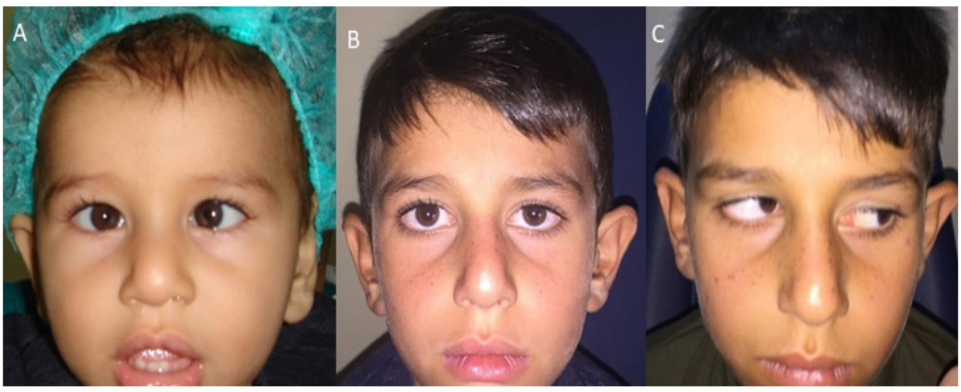

Figure 1: Chronological pictures of case 1. He had IOHF development in his 88th month post injection. He had 1.0/1.0 visual acuity. He underwent botulinum toxin injection when he was 8 months old. A shows the case has infantile esotropia in his 8th month. He was slightly around -0,5 D- hypermetropic in this age. He became orthophoric around 3-4 months post injection. B shows he is still ortophoric in his 7th year. C shows he has +2 IOHF. This patient was followed up until his 96th month. So, he is 8 years old in this image.

Figure 2: Chronological pictures of case 2. She had IOHF development in her 16th month. She had 0.4/0.6 visual acuity. She underwent botulinum toxin injection when she was 7 months old. A. Shows the case has infantile esotropia on her 7th month. She was +4.50/+4.50 D hypermetropic in this age. B. Shows she is ortophoric in her 5th month post injection. Her left eye stayed align first month, then deviated to outward until the 3rd month. Left eye again regained alignment after the 4th month and stood aligned until the 7th month. After the 7th month, strabismus of this patient returned to left monocular esotropia. After the 9th month, alternan esotropia and +1 IOHF developed. In the meanwhile, right eye behaved as the dominant eye. During her regular follow-up until her 16th month, the parents were instructed to patch the right eye either in the exotropia or in the esotropia phases. C. Shows she has an alternan esotropia and IOHF. D shows she has a high accommodative convergence component that can be corrected partially by eyeglass. Her accommodative component was corresponding with high accommodative convergence. Her cycloplegic refraction was +2.0+1.0x120/+2.0. D. This patient was in her 81st months in the image.

Figure 3: Chronological pictures of case 3. She underwent botulinum toxin injection when she was 6 months old. She had an IOHF that became apparent in her 13th month. A. Shows the case has infantile esotropia in her 6th month. She was found emmetropic. B. Shows she has consecutive exotropia in the left eye in post-injection 2nd month. So, patching on the right eye was applied in this stage. C. Shows the case in her post-injection 3rd month. Consecutive exotropia was recovered and now she is orthophoric. D. Shows she is still orthophoric in her 32nd month. E and F show she is still orthophoric and has +1 IOHF; she is in her 81st month. Her last cycloplegic refraction was detected as +2,0/+1,0 +1.0x90 and she described 0.2/0.2 visual acuity.

Figure 4: Chronological pictures of case 4. He had ended up with monocular esotropia. He had 0.1/1.0 visual acuity. He underwent botulinum toxin injection when he was 6 months old. A. Shows the case has infantile esotropia on his 6th month. His cycloplegic refraction was detected as 3,25+1,25x90/4,25+1,25x35 and left eye seemed as the dominant eye. So, patching on the left eye and eyeglass wearing were applied in this stage. B. Shows he is ortophoric in his 1st week post injection. C. Shows consecutive exotropia developed in the right eye in the 2nd week. His exotropia had lasted until his last regular follow-up (up to 3rd month post injection). Most probably, regain of alignment occured after the 3rd month. When strabismus returned to esotropia and when IOHF development happened are not known in this patient. He was determined as emmetropic in his 9th month. During his regular follow-up until his 9th month, the parents were instructed to patch the left eye. D. Shows he has a right monocular esotropia and +2 IOHF. This patient was in his 78th months in the image.

Figure 5: Chronological pictures of case 5. He had ended up with monocular esotropia. He had 1.0/0.1 visual acuity. He underwent botulinum toxin injection when he was 9 months old. A. Shows the case has infantile esotropia on his 9th month. His cycloplegic refraction was detected as 2,50/2,50 and right eye seemed as the dominant eye. So, patching on the right eye was applied in this stage. B. Shows he is ortophoric post-injection 9th month. C. Shows he has left monocular esotropia. He is in his 72nd month in the image. D. Shows he has +1 IOHF. When strabismus returned to esotropia and when IOHF development happened are not known in this patient. His cycloplegic refraction was detected as +0,75 0,75x50/0,75 0,50x135 in his 72nd month. During his regular follow-up until his 18th month, the parents were instructed to patch the right eye.

It was found the patients who is noncompliant with their follow-ups had received inadequate vision therapy (eye patches or wearing glasses if needed) when they were inquired in their late examinations.

A transient ptosis and sub-conjunctival hemorrhage from needle insertion developed in all the patients. Ptosis persisted for 2-3 weeks. It was not so severe as much as to occlude the pupil and to be a cause of amblyopia in any patient. Sub-conjunctival hemorrhage resolved between one to two weeks. The key clinical details over time were summarised in Table 1.

Discussion

In experimental animal study, -despite having controversy on optimum age of surgical alignment- earlier surgical alignment provides a better developed neurophysiologic matrix for binocular result [7-11]. A clinical investigational study was done by Ing, in furtherance of the experimental studies. Ing did report that despite a good motor alignment, patients who were aligned after 24 months of age demonstrated a significantly lower evidence of binocularity [2]. And he suggests that alignment should be accomplished by 2 years of age in infantile esotropic patients [2]. The preference of most strabismus specialists is of surgery for achieving the alignment before 2 years of age because botulinum toxin effect is not predictable [12]. Even if, botulinum toxin is preferred; there is no consensus on implemented dose and implementation way [12]. An interesting result of a meta-analysis done by Issaho DC is on dose response. They observed an inverse association between the dose of botulinum toxin. For every 1 IU increased in the mean dose, there was a reduction of 0.1% in the success rate [12]. Besides, some authors used the transconjunctival technique with EMG assistance in the procedures [13-16] while others opted for no EMG assistance [17-20]. Nevertheless, the reported success rates of botulinum toxin injection were 68-76%, as high as the surgical success rate [20-23]. Although there is a scarcity on comparative studies between botulinum toxin injection versus muscle surgery, results are in botulinum toxin injection's favour [20]. These facts are confirmed in a prospective study [24]: They did report that botulinum toxin injection is as effective as surgery before the age of 24 months. This fact was pointed out by Von Noorden: A precise examination may be impossible for a child under age of 12 months. So, the age of initial adequate alignment can not be determined exactly for patients who undergo surgery. And alignment may be achieved late after initial surgery [25]. This is also true for patients who receive botulinum toxin. Because an adequate dose adjustment for each and every one have not been achieved to date in literature. As a result, exotropia developed in all of the patients of this study. On the other end of this argument, Campos did report that exotropia after the first injection was a good predictor of success because consecutive exotropia confirms that the implemented dose is enough [26]. So we can say a 5 IU of botulinum toxin is enough for children younger 10 months old. This amount of dose was confirmed in another way in a comparative study: Botulinum toxin in initial was given 4 IU -just 1 IU less than the used dose of this study- in this study and they did report that consecutive exotropia did not develop in any patient of the botulinum group [20]. Development of consecutive exotropia after botulinum toxin injection also confirms that the injection is done to right place and it can be used as a sign instead of EMG guidance if it is not available.

Transient ptosis and IOHF developed in all the patients of this study. This rate is the worst ever reported [13]. Mild transient ptosis may be attributed to overdose but in some way it seems inevitable. Because, even with a less dose it can develop [20]. But, IOHF development in all the patients can not be attributed to botulinum dose or the nature of infantile esotropia. Despite that, DVD and nistagmus did not develop in any patient. When all these consequences such as presence of IOHF and absence of DVD and nistagmus are taken into account in this select case series, a monocular esotropia with a 1.0 visual acuity in dominant eye or a vertical strabismus with a 1.0/1.0 visual acuity are features of acquired esotropia rather than of infantile esotropia. Infantile esotropia accompanies DVD by 50%-90%, IOHF by 70%, latent nystagmus by 40%, and optokinetic asymmetry [27]. These are the most consequences of infantile esotropia even in surgically aligned patients. Because infantile esotropia occurs in a more sensitive period in term of visual maturation. Amblypia or absence of stereopsis can be more profound than acquired esotropia [28]. So, if the child can be kept in align by botulinum toxin and if rectus muscles are not to be disturbed by invasive corrections, because rectus muscles are in maturation phase in infancy, DVD or latent nistagmus can be prevented as shown in this series. Even more, patients can achieve a 1.0/1.0 visual acuity if they receive adequate vision therapy as exampled in case 1. Because the main success of botulinum toxin injection is underlied by mechanisms other than the direct mechanism of its action. The change in alignment after injected botulinum toxin brings the eyes to an acceptable anatomic range. Then binocular visual system establishes and gets to function. While the direct effects of botulinum toxin slowly dissipates, the binocular system starts to receive feedbacks from disparities in the motor alignment. Thus, rebooting the binocular visual system sustains motor fusion and maintains alignment [29]. This mechanism makes botulinum toxin injection more advantageous than surgical alignment. But, as Campos did report, infants around the age of 6.5 months respond this mechanism the best [26]. Because contracture in the medial rectus muscles increase over time [24]. And it can be said that botulinum toxin injection can reboot binocularity, prevent infants from rectus muscles' motor imbalance during visual maturation period, and carry the infant to a less sensitive period in term of visual maturation. And it can be asserted that if the infants had been compliant in their follow-ups and receive adequate vision therapy they would have a better chance in developing orthophoria. By this effort infantile esotropia can be changed into a more manageble form. The highlight of this study is that infantile esotropia management should be divided in two periods: Beginning, infant's strabismus should be aligned by botulinum toxin until an age when precise examination can be done and until sensory and motor visual system maturate. Later, it should be managed as an acquired esotropia. However, the results of a single and small case series provides limited evidence to support or refute this suggestion as an effective management option for infantile esotropia. Future retrospective or prospective studies with a larger number of participants and with fewer methodological limitations and biases are necessary.

Limitations

This study has a number of limitations: This series is the work of one surgeon. So the treatment decisions and follow-up appointments were determined by the one surgeon. Most likely, some patients who have kept ocular alignment had needed less vision therapy while the patiens who ended up with monocular esotropia had needed more vision therapy. As a consequence, some patients, in some way, missed out of adequate vision ther-

apy. As such, the effect of vision therapy in treatment strategy was not standardized. Therefore, this needs to be further studied in larger series, done by more than one surgeon, of patients that had standardized vision therapy and regular follow-ups.

Also, this study focused on just motor response and did not test for fusion. So a comment on the fusions of the patients who became orthophoric cannot be done. On the other hand, the study's children were younger than 10 months when they received botulinum toxin and they received a uniform single dose such as 5 IU in each muscle. Also they had a follow-up in their 6^{th}-8^{th} year. So, this study was able to report a very late situation of very select children with infantile esotropia. From this aspect, this study is of unique in the literature.

Conclusion

It seems that botulinum toxin injection gives a chance for the restoration of visual immaturity, and by this way infantile esotropia can be changed into a more manageble form.

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