American Journal of Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Botulinum Toxin Injections in Infantile Esotropia: Management Strategies in A Case Series

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***To Cite This Article:** Süleyman Çiftçi*. Botulinum Toxin Injections in Infantile Esotropia: Management Strategies in A Case Series. Am J Biomed Sci & Res. 2024 25(2) AJBSR.MS.ID.003292,* DOI: 10.34297/AJBSR.2024.25.003292

Received: December 09, 2024; **Published:** December 16, 2024

Abstract

Purpose: To investigate the impact of a single dose of botulinum toxin on infantile esotropia.

Methods: This retrospective observational case series reviewed data from infants with esotropia who received 5 IU/0.05 mL botulinum toxin in both medial rectus muscles without EMG control. The study included five patients and any complications related to the injection or the toxin itself were documented. Throughout their regular follow-up, parents were instructed to patch the dominant eye whenever fixation preference was observed, whether in the exotropia or esotropia phase. The patients underwent examinations between their 78th and 96th months to evaluate their current visual acuity and identify any late-term accompanying squints, nystagmus, or signs of amblyopia. Best-corrected visual acuity was assessed using Snellen optotypes or pictures.

Results: Five patients were included in the study. Inferior oblique muscle hyperfunction developed postinjection in all patients, occurring as early as the 7th month and as late as the 88th month. During the final examination, visual acuity was assessed. Among those with orthophoria, one patient exhibited 1.0/1.0 visual acuity, another had 0.4/0.6 visual acuity, and one had 0.2/0.2 visual acuity. In patients with monocular esotropia, the strabismic eye had a visual acuity of 0.1, while the dominant eye had a visual acuity of 1.0. Notably, none of the patients developed Dissociated Vertical Deviations (DVD) or latent nystagmus.

Conclusions: When infantile esotropia is managed with timely botulinum toxin injection, during the sensitive period, the binocular visual system might reset and potentially prevent motor imbalance during the visual maturation period.

Keywords: Infantile esotropia, Botulinum toxin injection, DVD, monofixation syndrome, latent nystagmus

Introduction

The exact cause of infantile esotropia remains uncertain. Many believe that this is due to a congenital defect, that causes constant fusion issues, and surgery is done for cosmetic purposes [1]. However, some argue that poor fusion could be a sensory adaptation caused by motor misalignment, suggesting the need for early surgery [2]. This uncertainty prompts the question: Could botulinum toxin injection offer insights? To the best of the author's knowledge, botulinum toxin has been studied as an alternative to surgical correction. Clinical analysis of the use of botulinum toxin injections to sort out congenital defects from sensory adaptations, and potentially delay surgical correction without sacrificing its benefits, has never been studied. In this case series, the author showed that botulinum toxin injections were able to delay surgical correction and that some patients were able to achieve orthophoria. By this means, an analysis of the long-term effects of botulinum toxin on sensory adaptation and motor misalignment can be performed separately.

Materials and Methods

This single-center retrospective study involved consecutive patients who received injections from the same surgeon between February 2013 and January 2015, with follow-ups in their 6th to 8th years. Institutional Ethics Committee approval was obtained (number 924, November 5th, 2021), and the Declaration of Helsinki was followed. Parents' consent was also obtained for using figures accompanying this paper. Individuals with preexisting neurological disorders or follow-ups lasting no longer than one-month postinjection, as well as those with concurrent eye diseases or a history of strabismus surgery before or after the postinjection, were excluded. Patients who received botulinum toxin injections between 6 and 9 months without further interventions were studied. Then, all the patients could be seen in their 6th-8th years. Initial ophthalmological exams included various tests, including the Hirschberg corneal reflex test, Doll's eyes reflex test, fixation preference test, cycloplegic refraction test using 1.0% cyclopentolate hydrochloride, fundus inspection, and ocular motility test. Ocular motility examination involved assessments of Dissociated Vertical Deviation (DVD), Inferior Oblique Muscle Hyperfunction (IOHF), and latent nystagmus. Patients with refractive errors were provided with eyeglasses. Those showing no change in their esotropic angle after wearing eyeglasses were classified as having infantile esotropia. The main outcomes included the development of orthophoria, visual acuity, and the incidence of DVD, IOHF, and latent nystagmus.

Botulinum toxin type A injections (50 units, diluted to 5 IU/0.05 mL) were used to target the medial rectus muscles under general anesthesia. Injections were administered using an insulin syringe and a 27-gauge needle without electromyography control. The study involved five patients, each with varying follow-up periods. Injection-related issues were recorded. Parents were instructed to patch the dominant eye if a fixation preference was observed in either the exotropia or esotropia phase. Between the 72nd and 96th months, new patient examinations involving assessments of current visual acuity, orthophoria status, late-term accompanying squints, nystagmus, and amblyopia were conducted. Best-corrected visual acuity was determined using Snellen optotypes or pictures.

Results

Clinical findings from nine patients who received botulinum toxin injections between February 2013 and January 2015 were assessed. Four patients were excluded due to prior and posterior surgeries (such as congenital cataract surgery before the injection or late strabismus surgery) or inadequate follow-up, leaving five patients for analysis. The key clinical details are summarized in (Table 1).

Table 1: Table of all the infants with key clinical details over time.

cases	1	2	3	4	5
Age of injection (months)	8	7	6	6	9
Age of strabismus onset (months)*	2	3	0,5	1	6
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 taken to achieve orthophoria post-injection	04-Mar	7	3	none	none
Endeavor of the parents to compliance to management of strabismus	strong	moderate	strong	poor	poor-moderate

Note*: Unit of time and age are set to month *= The time was reported by the parents approximately.

After the injections, all patients initially experienced temporary orthophoria for the first few weeks, followed by temporary exotropia. Subsequently, orthophoria reappeared in the first and 3rd-4th months. At the final examination (between the 72nd and 96th months), two patients showed orthophoria, two had monocular esotropia, and one had alternating esotropia partially corrected by eyeglasses. Inferior oblique muscle hyperfunction developed post-injection in all patients, occurring as early as the 7th month and as late as the 88th month. Among patients with monocular esotropia, the precise timing of the development of IOHF could not be determined due to noncompliance with follow-up. Unexpectedly, dissociated deviations and latent nystagmus, common in infantile esotropia, were absent in all patients. It was discovered that the patients who were noncompliant with their follow-ups had received inadequate vision therapy (such as eye patches or glasses when necessary), as revealed during their later examinations. Transient ptosis and subconjunctival hemorrhage occurred in all patients postinjection; however, these complications were not severe enough to cause amblyopia or pupil occlusion. Chronological images of the patients are shown in (Figures 1-5).

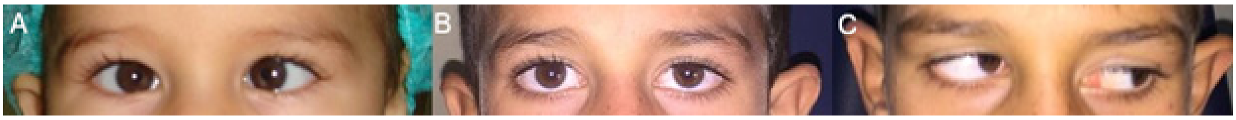

Figure 1: Chronological images of patient 1 are shown. He developed IOHF 80 months after the injection. At the time, he had a visual acuity of 1.0/1.0. He underwent botulinum toxin injection when he was 8 months old. Picture A shows that the patient experienced infantile esotropia in his 8th month. At that age, he was slightly hypermetropic, at approximately +0.5 D. He became orthophoric at approximately 3-4 months postinjection, as depicted in Picture B, where he remained orthophoric in his 7th year. Picture C shows that he developed +2 IOHF. This patient was followed up until the 96th month, at which point he was 8 years old according to imaging.

Figure 2: Chronological images of patient 2 are shown. She developed IOHF in her 16th month, with a visual acuity of 0.4/0.6. At 7 months of age, she underwent botulinum toxin injection. Picture A displays infantile esotropia in her 7th month, with a +4.50/+4.50 D hypermetropic condition. Picture B shows her orthophoric state at 5 months postinjection. Initially, her left eye aligned and then deviated outwards until the 3rd month. Alignment was regained after the 4th month and remained until the 7th month postinjection. However, after this period, the patient's strabismus returned to the left monocular esotropia. By the 9th month postinjection, alternating esotropia and +1 IOHF had developed. During regular follow-ups until her 16th month, the parents were advised to patch the right eye in either the exotropia or esotropia phase. Picture C illustrates her alternate esotropia and IOHF, while Picture D shows a high accommodative convergence component partially corrected by eyeglasses. Her cycloplegia refraction was +2.0 +1.0x120/+2.0 D. In the image, the patient was in her 81st month.

Figure 3: Chronological images of patient 3 are shown. She received a botulinum toxin injection at 6 months of age, with an IOHF becoming apparent in her 13th month. Picture A depicts infantile esotropia in her 6th month. Picture B displays consecutive exotropia in her left eye during the 2nd month postinjection, suggesting patching of the right eye at this stage. Picture C represents her condition at 3 months postinjection, showing recovery from subsequent exotropia resulting in orthophoria. Picture D illustrates her continued orthophoric state in her 32nd month. Pictures E and F show her ongoing orthophoria with +1 IOHF; she is seen in her 81st month. Her last cycloplegia refraction was +2.0/+1.0 +1.0x90, and she reported a visual acuity of 0.2/0.2.

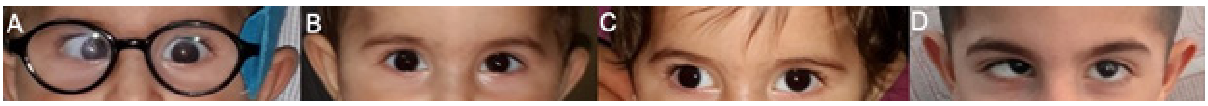

Figure 4: Chronological images of patient 4 are shown. He developed monocular esotropia with a visual acuity of 0.1/1.0 and received botulinum toxin injection at 6 months of age. Picture A shows infantile esotropia at 6 months, with a cycloplegia refraction of 3.25 +1.25x90/4.25 +1.25x35, indicating that the left eye was dominant. Patching on the left eye and eyeglasses was initiated. Picture B illustrates orthophoria at 1 week postinjection. However, Picture C displays a consecutive phase of exotropia in the right eye during the 2nd week, which persisted until the last regular follow-up (up to the 3rd month postinjection). Alignment likely resumed after the 3rd month, but the timing of the return to esotropia and IOHF development remains unknown. Emmetropia was confirmed in his 9th month. Throughout regular follow-ups until then, parents were instructed to patch the left eye. Picture D shows right monocular esotropia and +2 IOHF. The image shows the patient at 78 months.

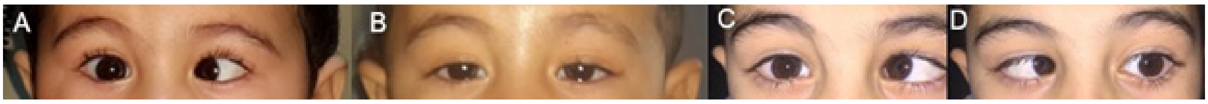

Figure 5: Chronological images of patient 5 are shown. He developed monocular esotropia with a visual acuity of 1.0/0.1 and received botulinum toxin injection at 9 months of age. Picture A displays infantile esotropia at 9 months, with a cycloplegic refraction of 2.50/2.50, indicating that the right eye was dominant, leading to patching of the right eye. Picture B illustrates orthophoria at 9 months postinjection. However, Picture C reveals left monocular esotropia. The image shows the patient at 72 months, with Picture D showing +1 IOHF. The timing of the return to esotropia and IOHF development is unknown. His cycloplegia refraction in the 72nd month was +0.75 0.75x50/0.75 0.50x135. During regular follow-ups until his 18th month, his parents were instructed to patch the right eye.

Discussion

Ing's clinical study revealed an intriguing finding: patients who were aligned after 24 months showed notably less evidence of binocularity, despite achieving satisfactory motor alignment [1]. This finding aligns with the findings of an experimental animal study suggesting that early surgical intervention contributes to a more advanced neurophysiological framework for binocular outcomes [3]. However, precise examinations of infants between 6 and 12 months of age are likely to be challenging. Consequently, performing surgery based on insufficient information could lead to a greater frequency of overcorrections and under corrections. As a result, such outcomes may deter surgery from its original purpose [4], causing immunofixation syndrome [5] and resulting in latent nystagmus [6]. To improve vision in the fixing eye in latent nystagmus, asymmetric convergence occurs but also results in an unavoidable and undesirable elevation of the fellow eye, which we recognize as DVD [6]. In this series, neither latent nystagmus nor DVD developed. This may be because the intervention was performed during the critical period of visual cortex development. Tychsen suggested that ophthalmic surgeons realign the eyes to within an envelope of 2.5 to 5.0 degrees within 60 days after the onset of strabismus. Accordingly, interventions should be tailored to the age of onset and not chronological age [5]. The age of strabismus onset reported in this series is not very reliable, but approximate ages were reported by parents. In Patient 5, the parents reported that their baby had experienced strabismus since birth. This confusion arises from the uninterrupted period between the baby's settlement of Hering's reflex and the onset of strabismus. Some parents have recently noticed strabismus but cannot provide a precise onset age. Therefore, the age of strabismus onset was approximate. However, the intervention was performed in three patients within two months of strabismus onset (patients 1, 3, and 4). Two of these patients achieved orthophoria, whereas the third exhibited suppression in the right eye due to insufficient parental compliance. Patient 2 had an accommodative component as well, and ultimately, this patient developed orthophoria through hypermetropia correction and achieved binocularity. Patient 5 required the most intensive patching of the dominant eye. However, the parents were most likely not up to this difficult task, so the right eye remained dominant, and the left eye remained suppressed.

The author does not recommend the management of infantile esotropia solely through botulinum toxin injection. Instead, the author proposed botulinum toxin injection if the patient experienced strabismus within 60 days of onset. This is because the change in alignment after the injection of botulinum toxin brings the eyes within an acceptable anatomical range. Subsequently, the binocular visual system is established and begins functioning. As the direct effects of botulinum toxin gradually dissipate, the binocular system starts receiving feedback from disparities in motor alignment. This reboot of the binocular visual system sustains motor fusion and maintains alignment [7].

Additionally, if the rectus muscles, which are in a phase of maturation during infancy, are not disturbed by invasive surgical corrections, infants around the age of 6.5 months respond best to this mechanism [8] because contracture in the medial rectus muscles increases over time [9] and surgical correction disrupts the structure. This approach could provide more accurate surgical correction over time and prevent patients from being affected by immunofixation syndrome, latent nystagmus, and DVD.

In contrast to the absence of latent nystagmus and DVD, IOHF developed in all the patients. The highest IOHF reports in the literature are by Hiles et al. and Wilson and Parks [10,11]. Both reports could detect the range of time but could not explain its main cause. Wilson says that IOHF is a true mystery in strabismus [11]. Hiles et al. reported that the incidence of IOHF was 78% in their study and noted that the greatest occurrence was during years 3 and 7 [10]. Wilson and Parks reported that the incidence of IOHF was 71%, and IOHF was most commonly detected in individuals aged 1 to 3 years [11]. Lee, et al,. also reported that the median age at the development of IOHF was 3 years [12]. The time of occurrence of IOHF in this series is consistent with others. However, as a different finding, patients with better visual acuity displayed the development of IOHF at a later stage, suggesting an inverse relationship between the age of onset of IOHF and the observed visual acuity. Although any explanation about the cause of IOHF development will be solely a comment, the author's perspective is that since all the reported literature about the time of the occurrence of IOHF is coherent, it raises a thought. In infantile esotropia, IOHF may not be an isolated disorder; instead, it may be a component of rectus discordance that affects the horizontal rectus muscle at one age and the inferior oblique muscle at another age.

The sensorial evolution of the patients in this series resulted in binocular vision or suppression of one eye. Monofixation syndrome and its consequences, such as latent nystagmus and DVD, did not occur in any patient. Although the author cannot prove that these patients did not have any deficits in sensory adaptation, the fact that all the patients eventually showed signs of visual maturation supports the idea that visual faults secondary to infantile esotropia are most likely not due to a congenital defect. Rather, they are secondary adaptations to poor fusion and motor misalignment.

This series is the work of one surgeon. Some patients in this series missed their follow-up appointments at times; otherwise, they would never have been left without further intervention. Some parents missed follow-up appointments for more than three years; however, the surgeon was eventually able to reach them and bring them back under control. In this respect, this study consists of long-term findings of a single botulinum injection for infantile esotropia, similar to a consequential fate report. Some patients most likely missed adequate vision therapy and developed suppression in one eye. On the other hand, if they had not missed adequate vision therapy, the results of a single botulinum toxin injection could have been better. In addition, the absence of control groups, including patients with esotropia who were injected after two years of age or those treated with standard muscle surgery, is the main limitation of this study.

Conclusion

This study emphasized that infants who are receiving botulinum toxin injections may avoid complications such as DVD or latent nystagmus. When infantile esotropia develops around the age of 6.5 months, during the sensitive period, and if it is managed with timely botulinum toxin injection, the binocular visual system might reset and potentially prevent motor imbalance during the visual maturation period. This suggests that botulinum toxin might offer advantages beyond surgical alignment alone by rebooting binocularity and aiding in the maintenance of motor fusion. It provides a two-phase management approach: initial alignment using botulinum toxin until a more precise assessment can be performed and muscle maturation can occur, followed by a later stage focused on surgical management.

Ethics Statement

In this case series, images were obtained during follow-up from consecutive patients treated for infantile esotropia at Diyarbakir Gazi Yasargil Training and Research Hospital between February 2013 and January 2015. The study was conducted in accordance with the tenets of the 2013 revision of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Diyarbakir Gazi Yasargil Training and Research Hospital (number 924, November 5th, 2021). The parents received appropriate explanations and gave written informed consent to participation.

Data Availability Statement

The main data to support the conclusions have been provided. All other associated data have been deposited into

*https://drive.google.com/drive/folders/1x99_LAKCxE3V-8K55OMXZqcGXlhImsYQm?usp=*sharing and can be accessed after requesting permission from me.

Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

While preparing this work, the author used ChatGPT 3.5, Grammarly, and Curie to check punctuation, syntax errors, and the flow of the phrases. The author edited the content as needed. After using this tool, the author reviewed and edited the content as needed and took full responsibility for the publication's content.

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