

Long-Term Effects of Botulinum Toxin in Large-Angle Infantile Esotropia

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Purpose: The purpose of this study is the motor outcome analysis of early Botulinum toxin (BT) treatment in patients affected by large-angle infantile esotropia (IE).

Patients and Methods: Retrospective analysis of 130 medical charts of IE patients who underwent BT injections between 2004 and 2019 was performed. All patients underwent BT injections within 13 months of age.

Results: Thirty patients, matching the inclusion criteria, were included in the study. Twenty-eight patients showing residual ET ≥ 25 PD (34.3 \pm 6.6 PD ranged from 25 to 50) underwent surgery.

Conclusion: Our result after 1 Botulinum toxin injection showed a very low success rate (6.7%) at last follow-up (28.3 \pm 7.2 months). Our data would suggest one Botulinum toxin injection in children affected by large-angle infantile esotropia allows a significant reduction of deviation but does not avoid the need for surgical treatment.

Keywords: strabismus, pediatric, congenital

Introduction

Infantile esotropia (IE) is defined as an early-onset esodeviation, usually within 6 months of age, with an estimated incidence of 0.1–1.0%.^{1–5} Although the role of visual cortex and cortico-mesencephalic-cerebellar pathways has been proposed, the etiology of IE is still unknown.⁶

In order to achieve satisfactory motor and sensory outcome in IE patients, some authors recommend first surgery between 2 and 4 years of age, after the appropriate treatment of amblyopia.⁷ Since 1980, the encouraging results obtained by using the transitory medial rectus (MR) muscles denervation induced by Botulinum toxin (BT) injection in patients affected by IE, made this procedure a reliable alternative to the surgical one, though more debatable results are reported (Table 1).^{8–19}

The purpose of this study is the motor outcome analysis of early BT treatment in patients affected by large-angle IE.

Patients and Methods

Retrospective analysis of 130 medical charts of IE patients who underwent BT injections between 2004 and 2019 was performed. All patients underwent extensive ophthalmological and orthoptic examination according to the patients' age and cooperation including best corrected visual acuity (BCVA) using 5 meters Landolt C or Albin E charts, cycloplegic refraction (atropine 0.5%), Krimsky and/or Hirschberg tests, cover, cover-uncover and prismatic alternating cover test,

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Table 1 Results reported by other studies

Year	Authors	Pt. N.	F-U Time Range*	Inj. N.	Mean Age* 1th Inj. and/or Range	Toxin IU	Pre Inj. Deviation# Mean (Range if Aval.)	Success Rate
2018	Solebo et al. ¹⁹	10	7–100	1	10 (5–166)	2.5	40 (18–80)	20%
2017	Speeg-Schatz et al. ¹⁸	65	24–96	1	15 (9–26)	10	40 (20–60)	67.3%
2012	Gursoy et al. ¹⁷	25	75–89	1–2	10 (9–13.5)	4–2.5	40 (35–45)	68%
2010	de Alba Campomanes et al. ¹⁶	322	6–36	1–3	16.6 (8–24)	5–7.5	38 (11.7 SD)	45%
2008	Thouvenin et al. ¹⁵	74	24–84	1–2	18 (7–36)	5	>20	65%
2006	Toledo and Saucedo ¹⁴	51	12	1–2	13.7 (6–24)	5–7.5	45 (20–90)	74%
2004	Spielmann ¹³	19	18–84	1	8.15 (5–13)	2–3	52.7 (10–100)	10%
2000	Campos et al. ¹²	60	60	1	5–8	2.5–3	35	88%
1997	McNeer et al. ¹¹	76	36	1–3	16 (4–48)	2.5	33 (10–60)	89%
1992	Ing ¹⁰	12	36	1–3	7.7 (4–21)	1.25–6.25	41 (10–70)	50%
1989	Biglan et al. ⁹	12	22,6	1–2	6–360	1–12.5	26	33%
1989	Scott et al. ⁸	58	26	1–3	4–96	1–12.5	43	66%

Notes: *Months, #Prism Diopters.

Abbreviations: Pt, N, patients numerosity; F-U, follow-up; Inj. N, number of injections; IU, International Units; Pre Inj. Deviation, deviation before first injection.

doll's head maneuver, Worth 4-dot test, TNO stereotest, biomicroscopy and fundus examination.

Inclusion criteria were: large-angle esotropia, ≥ 40 prism diopters (PD) diagnosed within 6 months of age, hyperopic spherical equivalent (SE) within 3D, follow-up > 5 years, BT injection within 13 months of age. Patients showing nystagmus, upshoot, duction limitation, dissociated vertical or horizontal deviation (DVD/DHD), A-V pattern, accommodative component, neurological or systemic disease, ocular abnormalities or previous ocular surgery were excluded from the study.

Botulinum toxin A (Botox; Allergan, Irvine, CA) injection was administered under general anesthesia (sevoflurane inhalation) using a 27-gauge needle on an insulin syringe after conjunctival limbal incision and MR isolation, without electromyographic guidance. Bilateral medial rectus injections of 5 IU in 0.25 mL of saline for deviations between 40 and 50 PD and 7 IU in 0.35 mL for deviations greater than 50 PD were performed.

Residual esotropia ≥ 20 PD in patients beyond 24 months of age were surgically treated according to the Helveston recommendations.²⁰

Written informed consent for treatment and to review the patient's medical records for research purposes was provided by parents or legal guardians before each treatment for all patients. The study followed the tenets of the Declaration of Helsinki. Ethical approval for the protocol was obtained from the Institutional Review Board of University of Salerno.

Results

Thirty patients, matching the inclusion criteria, were included in the study. Clinical and demographic data are shown in Table 2.

All patients underwent BT injection within 13 months of age with a mean follow-up period of 28.3 ± 7.2 months (ranged from 19 to 43). At 1 month post-injection examination, all patients showed a significant reduction of deviation (ranged from -20 to 25 PD); 5 patients were orthotropic (16.7%), 11 showed a consecutive XT (36.7%) and 14 showed residual ET (46.7%). Seventeen patients showed a residual deviation of ± 10 PD (success rate of 56.7%). At 6 months follow-up the success rate decreased to 6.7% and was unvaried at the last follow-up (28.3 ± 12.4 months). Mean deviation from baseline to last follow-up decreased by 20.3 ± 13.3 (ranged from 0 to 60).

Twenty-eight patients showing residual ET ≥ 25 PD (34.3 ± 6.6 PD ranged from 25 to 50) underwent surgery. At 6 months and 3 years after surgery follow-up mean deviation was 3.9 ± 9.3 PD (ranged from -18 to 10) and 4.1 ± 8.5 PD (ranged -12 to 14), respectively.

At the final examination, 28 patients (93.3%) showed monocular or alternating suppression, 7 (23.3%) showed gross stereopsis (> 480 arc) and 23 (76.7%) had no stereopsis.

Discussion

The effects of Botulinum toxin in patients affected by infantile esotropia represent a controversial issue. Previous literature data including age at injection, BT

Table 2 Demographic and Clinical Data

	Mean±sd	Range
Age at examination (months)	7.4±2.2	[4;12]
Baseline deviation (prism diopters)	52.3±7.6	[40;70]
Age at BT injection (months)	8.7±2.3	[5;13]
1 month follow-up deviation (prism diopters)	1.6±12.8	[-20;25]
6 months follow-up deviation (prism diopters)	28.2±12.4	[-10;55]
≥19 months follow-up deviation (prism diopters)	32±11.1	[-10;50]
Age at surgery (months)	36.9±6.6	[27;50]
12 months follow-up deviation (prism diopters)	4.6±8.6	[-18;12]
5 years follow-up deviation (prism diopters)	7.3±7.1	[-12;16]

dose, number of injections, amount of deviation and consequently results are extremely variable and, considering the lack of standards, the procedure settings actually rely on each surgeon (Table 1).

Although Campos et al.¹² reported patients treated at or before 6.5 months were more likely to respond favorably to BT treatment and Speeg-Schatz et al.¹⁸ reported a positive correlation between age at injection and post-operative angle, McNeer et al.¹¹ did not find any statistical difference between patients injected before and after 12 months of age even if his limited sample size needs to be considered. Moreover, multivariate analysis performed by de Alba Campomanes et al.¹⁶ in one of the largest prospective studies, showed the most important predictor of alignment was the preoperative amount of deviation. They reported a significant difference between the amount of deviation in patients who achieved satisfactory motor outcome and those who did not; independently by age at treatment and number of injections the success rate of $\leq 30\Delta$ esotropia BT-treated was not different than that of surgery. Thouvenin et al.¹⁵ reported similar results on 74 esotropic patients, describing that the only predictive factor of treatment failure was the presence of high adduction.

Early treatment of infantile esotropia should consider the spontaneous resolution rate, in infants under 9 months, of 27%, typically occurring in the intermittent or variable form of esotropia, and 9% in constant ones, as reported by PEDIG.²¹

In our study only constant, large-angle esotropia with no vertical deviation, injected before 13 months of age, were considered in order to minimize bias related to a wide range of baseline deviation, age at injection, recurrence of deviation due to vertical component/inferior oblique overaction or variable deviation due to associated accommodative component. Our results after 1 Botulinum toxin injection showed a very low success rate (6.7%) at last follow-up (28.3±7.2

months). Differences between our results and those describing success rates from 66% up to 89% (Table 1) might be partially explained by our strict inclusion criteria, especially the baseline deviation one. We found a mean reduction of baseline deviation (52±7.5; range 40–70 PD) of 19.3±11.2 PD at last follow up, significantly lower than 33 PD reported by McNeer et al. (who included multiple injection patients), but wide enough to justify, according to Campomanes et al., the efficacy of BT in the treatment of small-to-moderate angle esotropia. Although there are frequent complications of Botulinum toxin injections, such as transient ptosis, subconjunctival hemorrhage, and vertical deviation, no serious complication were observed in our series, but diffusion of the toxin was observed in 1 patient showing ptosis, which spontaneously resolved in 4 months. Exotropia as overcorrection is considered a desirable outcome of BT injection readjusting the fusion pathway though the visual feedback.¹² Exotropia was present in 7 patients (23.3%) at 6 months follow-up and in only 1 patient (3.3%) at the last one.

More than 90% of BT-treated patients showed a significant amount of esotropia requiring surgery.

Recession-resection procedure performed in a patient with more than 20 PD of residual esotropia, according to previous literature, showed a success rate of 78.5% and 64.3% at 6 months and 5 years follow-up, respectively. At final examination, patients with a residual deviation of 0 to +8 PD achieved a gross stereopsis (25%).

Despite the limitations of the study, such as limited sample size and lack of control group, this represents, to our knowledge, the first study focused exclusively on treatment of large-angle infantile esotropia treatment. Large-scale multicentre clinical trials using well established inclusion criteria would be very useful to clarify Botulinum toxin's effective role in infantile esotropia management.

Conclusion

In conclusion, our data would suggest one Botulinum toxin injection in children affected by large-angle infantile esotropia allows a significant reduction of deviation but does not avoid the need for surgical treatment.

Disclosure

The authors report no conflicts of interest in this work.

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