Long-Term Follow-up of Botulinum Toxin Injection in Treatment of Infantile Esotropia: Outcomes and Predictive Factors for Success

Eficácia a Longo Prazo da Injeção de Toxina Botulínica no Tratamento da Esotropia Infantil: Resultados e Fatores Preditivos de Sucesso

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ABSTRACT

INTRODUCTION: RInfantile esotropia (IE) is the most common type of childhood esodeviation. Its treatment goal is to achieve enough microtropia and isoacuity to provide binocular cooperation. Since botulinum toxin (BT) is rising as a less invasive treatment, we aim to evaluate its long-term results and determine if there are any predictive factors for success.

METHODS: We retrospectively reviewed infantile esotropia patients' records who had BT injections as a first-line treatment between 2017 and 2023 at our centre. We examined angles before and after the procedure, BCVA, binocular functions and the need for additional treatment. Complete success was defined as an angle ≤10 PD; partial as at least a 50% reduction but >10 PD, with other cases considered failures.

RESULTS: We included 101 patients with a mean age of 4.77±3.54 years. Mean preoperative deviation angle was 30±11.82 PD. A total of 58.4% of patients had isoacuity regarding BCVA. The change in the mean angle at 3, 6, 12 months and last obtained after procedure was 24.74±11.89 PD (*p*-value<0.001); 19;18±12.01 PD (*p*-value<0.001); 16.04±14;79 PD (*p*-value<0.001) and 15.67±12.70 PD (*p*-value<0.001) respectively. Microtropia at 3, 6, 12 months and last obtained was achieved in 73.3%, 45.5%, 24.8% and 25.6% respectively. Isoacuity was achieved in 64.4% of patients and binocular cooperation in 28% of cases. Twenty-four patients (23.8%) underwent a second injection and 19 patients (18.9%) needed secondary surgery. Early microtropia significantly increased the time needed to a new BT injection (*p*-value=0.005) as well as the need for secondary strabismus surgery (*p*-value=0.002). Simultaneously, receiving the first injection at an earlier age seemed to significantly influence last obtained BCVA (*p*-value=0.042) and binocular cooperation (*p*-value=0.023,) but not the degree of microtropia (*p*-value=0.588).

CONCLUSION: To the best of our knowledge, this is the largest European study concerning long-term follow-up of infantile esotropia after BT injection. We noted complete success in most cases, as well as improvements in binocular cooperation and isoacuity over time. These results continue to support the role of BT injection as a first-line treatment, as early as possible, potentially delaying surgery.

KEYWORDS: Botulinum Toxins, Type A; Child; Esotropia/drug therapy; Oculomotor Muscles.

RESUMO

INTRODUÇÃO: A esotropia infantil (EI) é o esodesvio mais comum na infância. O objetivo do tratamento é alcançar microtropia e isoacuidade, favorecendo a cooperação binocular. Neste estudo pretende-se avaliar os resultados a longo prazo do tratamento com toxina botulínica (TB) e identificar fatores preditores de sucesso.

MÉTODOS: Avaliamos retrospetivamente os doentes com EI tratados com toxina botulínica como primeira linha entre 2017 e 2023 no nosso centro. Avaliaram-se os ângulos do desvio antes e após o procedimento, máxima acuidade visual corrigida (MAVC) para longe, funções binoculares e a necessidade de tratamento adicional. Definiu-se sucesso completo como a obtenção de um ângulo ≤10 DP; sucesso parcial como uma redução ≥50%, mas >10 DP; e as restantes, insucesso terapêutico.

RESULTADOS: Foram analisados 101 pacientes (idade média: 4,77 ± 3,54 anos) com ângulo de desvio pré-operatório médio: 30 ± 1,82 DP. Inicialmente, 58,4% tinham isoacuidade visual. Após o procedimento, verificou-se uma alteração média de desvio aos 3, 6, 12 meses e no último obtido de 24,74±11,89 DP (*p-value*<0,001); 19,18±12,01 DP (*p-value*<0,001); 16,04±14,79 DP (*p-value*<0,001) e 15,67±12,70 DP (*p-value*<0,001), respectivamente. A microtropia foi alcançada aos 3, 6, 12 meses e na última avaliação em 73,3%, 45,5%, 24,8% e 25,6%, do casos, respetivamente. No final, 64,4% tinham isoacuidade e 28% cooperação binocular. 24 crianças (23,8%) receberam segunda injeção e 19 (18,9%) precisaram de cirurgia.

A obtenção de microtropia precocemente aumentou de forma significativa o tempo necessário para uma nova injeção de TB (*p-value*=0,005), bem como a necessidade de cirurgia secundária (*p-value*=0,002). Simultaneamente, verificou-se que o tratamento precoce influenciou significativamente a última MAVC obtida (*p-value*=0,042) e a cooperação binocular (*p-value*=0,023), mas não o grau de microtropia (*p-value*=0,588).

CONCLUSÃO: De acordo com a literatura existente, este parece ser até à data o maior estudo europeu no que diz respeito especificamente à eficácia a longo prazo da EI após a injeção de TB. Verificou-se sucesso completo na maioria dos casos, e uma evolução positiva na cooperação binocular e isoacuidade ao longo do tempo. Estes resultados continuam a enaltecer o papel da injeção de TB como terapêutica primária, potencialmente adiando a cirurgia.

PALAVRAS-CHAVE: Criança; Esotropia/tratamento farmacológico; Músculos Oculomotores; Toxinas Botulínicas Tipo A.

INTRODUCTION

Infantile esotropia (IE) is a disorder marked by the convergent misalignment of one or both eyes with its onset before 6 months of age, and it is the most common form of childhood esodeviation with an estimated incidence of 27 per 10 000 births.[1] By definition, it has its classic onset before 6 months of age, presenting with a constant and large angle deviation in otherwise healthy children. Current literature continues to suggest that early intervention provides benefits regarding motor and sensory outcomes, at the same time as botulinum toxin (BT) is gaining place as a less invasive treatment. botulinum toxin A is a toxin derived from *Clostridium botulinum* that inhibits acetylcholine release when injected into the muscle, resulting in muscle weakness or paralysis 3–5 days after the procedure. With treatment, the goal is to achieve some alignment of the visual axis that allows some degree of binocular cooperation that can persist or regress, needing further treatment. We then aim to evaluate the long-term results of BT injection in our centre as a first-line therapy for IE and to determine if there are any predictive factors for success.

MATERIAL AND METHODS

We retrospectively review all medical records from patients with infantile esotropia (ie) between 2017 and 2023 who underwent botulinum toxin (BT) injection in the medial rectus muscle as a first-line treatment. IE was defined as constant, stable esotropia, with age of onset being less than 6 months in neurologically normal and otherwise healthy children.

We then excluded all patients with ocular comorbidities and other possible biases such as concomitant nerve palsies or restrictive motility disorders, deprivation amblyopia, perinatal hypoxic-ischemic injuries, perinatal and post-natal neurological disorders, development delay and other anterior or posterior segment abnormalities. We assessed some specificities of the deviation, such as dissoci-

ated vertical deviation (DVD) and inferior oblique overaction (IOOA). We prescribed full optical correction after cycloplegia for all patients before treatment and handled strabismic amblyopia by occluding healthy eyes adapted to each case's severity. The BT treatment consisted of bilateral transconjunctival medial rectus injection of botulinum type A toxin (Botox, Allergan®) in a dose of 5 units in children older than 2 years old with a deviation >20 PD; 3.5 U in children older than 2 years old but with an angle <20 PD; and 2.5 units for children under two. The technique starts with diluting the product with 2 mL of 0.9% NaCl. Then, the eye is pulled to an abducted position with forceps grasping the conjunctiva, tenon and medial rectus. BT is then injected transconjunctivally into the muscle using a 27G needle. Post-operative care included treatment with antibiotic drops.

We measured BCVA and deviation angle before and after treatment (at 3 (3M), 6 (6M), 12 months (12M) and last obtained (LO) after the injection). BCVA was measured using Tumbling E´s or Lea Symbols charts, and the angle was measured wearing optical correction by prismatic cover test or Krimsky test. We also assessed the presence of binocular cooperation regarding simultaneous perception (through Worth´s lights, vectograph and synoptophore), as well as fusion capacity (through Worth´s lights, Bagolini´s striated glasses or synoptophore) and stereopsia (through Titmus test, vectograph and synoptophore). We also evaluated the need for a second injection, secondary surgery, and procedure-related complications. Regarding outcomes, we defined complete success as a final angle measuring ≤ 10 prismatic diopters (PD); partial success as the final deviation angle reduced to at least half of its original amount but >10 PD; and failure in all other cases. SPSS® software was used for statistical analysis. Confidence intervals were calculated at 95%, and a value of $p<0.05$ was considered statistically significant.

RESULTS

We included 101 patients, mostly females, corresponding to 52.47% (n=53) of cases. The mean age of our sample was 4.77 ± 3.54 years at first injection, with 9 patients presenting to the first appointment with ≥ 10 years of age and naïve of treatment. Botulinum toxin was still administered to these older patients, considering its less invasive nature, fewer complications, and availability at our centre, serving effectively as a therapeutic trial. Eight patients had IOOA, and 10 patients had DVD.

REFRACTIVE STATUS

Regarding refractive status, our sample had a pre-injection mean spherical equivalent (SE) of +1.93 ± 2.58 D. Of all patients, 12.87% were myopic; 48.51% (n=49) were mild hyperopic (SE <+3 D); 28.71% (n=29) were moderate hyperopic (SE 3-6 D); and 3.9% (n=4) were severely hyperopic (>+6 D).

ANGLE OF DEVIATION, ISOACUITY AND BINOCULAR COOPERATION

Before being submitted to the first BT injection, the mean esodeviation angle was 29.66±11.82 PD. From our sample, 58.41% of cases had BT injection dosing of 5U; 14.85% of children were injected with 2.5 U, and all other cases had 3.5 U. After treatment, we obtained at 3M a mean deviation angle of 3.30±8.65 PD; at 6M, an angle of 10.18±12.63 PD; at 12M, it was 11.71±12.39 PD, and the LO was 14.71±12.94 PD. Regarding microtropia and success rates, these results correspond to a complete success rate of 73.3% at 3M, 45.5% at 6M, 24.8% at 12M and 25.6% at LO (Table 1).

Table 1. Percentage of Microtropia Over Time.

Angle of Deviation	3M	6M	12M	LO
Microtropia	73.3% (n=74)	45.5% (n=46)	24.8% (n=25)	25.6% (n=26)
Absence of microtropia	26.7% (n=27)	54.45% (n=55)	75.24% (n=76)	74.26% (n=75)

Being injected at an early age can statistically influence success at 3M (p-value =0.042), but the effects dissipate over time. Regarding children older than 10 years on first appointment, isolated group analysis revealed that all of them obtained microtropia at 3M after treatment, 6 of them at 6M, 5 of them at 12M and 3 at LO. In this particular group of patients, only 1 (0.11%) reported having some form of binocular cooperation (simultaneous perception) at the end.

Concerning the children that presented IOOA (n=8) and/or DVD (n=10), only 2 of them (1 with DVD and 1 with IOOA) achieved microtropia at 3M.

Concerning doses, we found no difference between BT dosing of 5U, 3.5 U and 2.5 in achieving long-term microtropia at 3M (p-value= 0.062); 6M (p-value=0.108), 12M (p-value=0.530) and at LO (p-value=0.602).

Regarding refractive status, there was also no significant difference between mean SE and achieving microtropia at 3M (p-value=0.733), at 6M (p-value= 0.430), 12M (p-value=0.514) and at LO (p-value=0.997).

From children that obtained microtropia, we found that the ones who had higher angle deviation at first injection (≥30 DP) were less likely to achieve it compared to the ones who had a deviation angle less than 30 DP, at 3M (55% *vs* 75%), at 6M (51% *vs* 67.6%), at 12M (51.2% *vs* 63%) and LO (52% *vs* 62%), with difference getting less pronounced with time.

Regarding complications, 9.9% of patients had transient ptosis (n=10), and 17.82% (n=18) had transient exotropia following the first injection. Those children with exotropia had a statistically significantly higher chance of achieving microtropia 1 year after the procedure (p-value=0.012), suggesting that major responders in the first evaluation were more likely to maintain better alignment throughout time.

Before BT injection, 36.13% of children presented with isoacuity regarding BCVA, and 12% had some form of binocular cooperation. At the end we found that those values

had increased to 64.4% (*p*-value=0.042) and 28% (*p*-value=0.023), respectively.

SECONDI NJECTION AND SECONDARY SURGERY

Twenty-four patients (23.8%) underwent a second injection, and 19 patients (18.9%) needed secondary surgery to maintain a large angle of deviation or for relapsing. The mean time elapsed between the first and second injections was 16 months. Of patients who needed a second injection, 75% (n=18) of them had microtropia at 3M, with it being associated with a longer time until a second BT was needed (*p*-value= 0.005).

Regarding children who needed subsequent surgery, 89.47% had an initial deviation of ≥30 PD. We also found that achieving early microtropia at 3M was statistically associated with lower needs of subsequent surgery (*p*-value=0.002).

On the first appointment, 8 children had IOOA, and 10 children had DVD. In this group, 4 children (50%) with IOOA and 1 (10%) with DVD underwent subsequent surgical correction of the vertical component.

DISCUSSION

Our results demonstrated a complete success rate of 73.3% at 3M, corresponding to higher rates of early response compared to existing literature (Alam *et al*).[2] With time, the percentage of children with microtropia showed a declining tendency, following the trend of some authors, such as S. Koudsie *et al*[3] and S. Pansiero *et al*,[4] who reported microtropia rates at 6 months of 55.5% and 30.6%, respectively. Our results were somewhere in the middle (45.5%).

As opposed to Thouvenin *et al*,[5] McNee *et al*[6] and S.Koudsie *et al*,[3] who found that the age of the first injection did not seem to be a predictor factor for obtaining early microtropia, we concluded that there was a significant association between those parameters, with an earlier time of injection being associated with higher success rates, consistent with Campomanes *et al*.[7] In fact, we believe this is an important mark since obtaining microtropy in early ages enhances the chance of acquiring binocular cooperation. Regarding refracting status, mild hyperopia was the most frequent refractive error (48.51%) consistent with literature as described by Costenbader *et al*[8] (40%), but it did not seem to statistically influence success rates. On the other hand, we found that higher angles at presentation were associated with worse outcomes regarding success, as children with esodeviations ≥30 DP achieved microtropia less frequently in all evaluations. However, the difference between the two groups got less pronounced with time. Our results are consistent with those of Issaho *et al*,[9] as we both found that BT injection benefits mostly children with smaller angles.

In our study, 18.9% of patients had to be submitted to secondary surgery (consistent with existing literature of 26.7%,[3] 35%[5] and 25%[10]). Of those children, 89.47% had an initial deviation of ≥30 PD, suggesting once again that higher angles are a negative predictive factor for success.

Concerning the need for a new BT injection, we found that of the 19 patients needing it, 78% had achieved microtropia at first. Obtaining microtropia was not statistically associated with the need for a second injection, but it was with the mean time elapsed until the event (*p*-value=0.005).

BT can suffer diffusion within the orbital region, affecting nearby anatomical structures and leading to side effects. When administered into the medial rectus muscles, it induces paralysis and may result in an initial shift from esodeviation to exodeviation. Furthermore, BT can also disperse into the eyelid and vertical muscles, potentially causing symptoms such as ptosis or vertical deviation. However, in most cases, those effects are temporary and tend to disappear with time. Our study found transient ptosis in 9.9% of patients and exotropia in 17.82%. Those children with exotropia had a statistically significantly higher chance of achieving microtropia 1 year after the procedure (*p*-value=0.012), suggesting that major responders in the first evaluation were more likely to maintain better alignment throughout time. Thouvenin *et al*[5] described similar findings reinforcing that the proportion of the adduction following BT injection is also a predictive factor for success.

Before BT injection, 36.13% of children presented with isoacuity regarding BCVA, and 12% had some form of binocular cooperation. Those values increased to 64.4% (*p*-value=0.042) and 28% (*p*-value=0.023), respectively. These findings seem to reinforce the basis that improving visual axis alignment can make a difference in developing binocular functions and obtaining isoacuity.[11]

As a limitation, we highlight the fact that this is a retrospective study. Additionally, by being a center that provides care to a deprived and vulnerable population, some of the children (n=9) came to their first appointment at a more advanced age and were naive to treatment, becoming outliers when it comes to age. However, this restraint turned out to provide heterogeneity to our sample, proving that BT injection is relatively effective even in those cases, at least delaying further treatment by providing time of ocular alignment, although its effects of binocularity were modest.

To the best of our knowledge, this is the largest European study directly concerning long-term follow-up of infantile esotropia after BT injection. We believe that these results continue to support the role of BT injection as a first-line treatment, as early as possible, potentially delaying surgery.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

MV: Drafting the manuscript; critical review and final approval.

TC, CM, JA, SP, MJS, IP: Critical revision and final approval.

MV: Elaboração do manuscrito; revisão crítica e

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