Original article

Botulinum toxin type A as treatment of partially accommodative esotropia

E.M. Flores-Reyes, M.G. Castillo-López, R. Toledo-Silva, J. Vargas-Ortega, C.E. Murillo-Correa, A. Aguilar-Ruiz*

Departamento de Estrabismo, Instituto de Oftalmología Fundación “Conde de Valenciana” IAP, Mexico City, Mexico

ARTICLE INFO

Article history:
Received 28 February 2015
Accepted 3 November 2015
Available online 2 March 2016

Keywords:
Partially accommodative esotropia
Botulinum toxin type A
Amblyopia
Strabismus
Treatment
Residual deviation

ABSTRACT

Objective: To determine the effectiveness of a botulinum toxin type A injection in both medial rectus muscles in patients with partially accommodative esotropia. Residual deviation and stability of strabismus were evaluated at 18 months follow up.

Method: A prospective, analytical, quasi-experimental study was conducted on a cohort of 21 patients who underwent total cycloplegic refraction and with a residual deviation of at least 14 DP. A botulinum toxin type A dose of 5IU was injected into each medial rectus muscle for a residual deviation greater than 18 DP, with a dose of 2.5 IU being used for a deviation between 14 and 18 DP. Multivariate logistic regression analyses were performed to relate residual deviation to variables recorded as potential predictors.

Results: A total of 21 patients were included, 33.3% (n = 7) males and 66.6% (n = 14) females. Mean visual acuity was −0.28 ± 0.25 logMAR for right eye (range 0 to −1) and −0.42 ± 0.31 logMAR for left eye (range 0 to −1.3). Mean angle of residual deviation before application of botulinum toxin was 40.95 ± 8.6 DP without spectacles correction, and 22.3 ± 7.99 DP with full cycloplegic refraction. Adverse effects were ptosis in 14.2% (n = 3), diplopia 23.8% (n = 5), and vertical deviation in 33% (n = 7). One patient had a poor outcome, therefore required surgical treatment.

At one year follow up, 85.71% of patients showed good results with esotropia of 12 DP or less, dropping to 71.43% at 18 months of follow up.

Conclusion: Botulinum toxin type A is an effective long-term treatment with a good response in 71.43% of patients. No predictors of good response were demonstrated.

© 2015 Sociedad Española de Oftalmología. Published by Elsevier España, S.L.U. All rights reserved.


* Corresponding author.
E-mail address: dra.aguilarruiz@yahoo.com (A. Aguilar-Ruiz).

2173-5794/© 2015 Sociedad Española de Oftalmología. Published by Elsevier España, S.L.U. All rights reserved.
Uso de toxina botulínica A en el tratamiento de las endotropías parcialmente acomodativas

RESUMEN

Objetivo: Determinar la efectividad de la toxina botulínica (TB) tipo A aplicada en ambos rectos mediales en pacientes con endotropía parcialmente acomodativa (ETPA). Se evaluó la desviación residual y su estabilidad a 18 meses de seguimiento.

Método: Estudio analítico prospectivo, cuasi experimental. Se estudió una cohorte de 21 pacientes con uso de refracción ciclopéjica total con desviación residual igual o mayor a 14 DP. Se realizó aplicación de TB en ambos rectos mediales, 5 U de TB para desviaciones residuales mayores de 18 DP y 2,5 U para desviaciones residuales menores. El análisis incluyó regresión logística entre variables para considerar factores predictivos.

Resultados: Se incluyeron 21 pacientes, 33,3% pacientes (n = 7) del género masculino y 66,6% (n = 14) del género femenino. La capacidad visual promedio fue de -0,28 ± 0,25 logMAR ojo derecho (rango 0 a −1) y −0,2 ± 0,31 logMAR ojo izquierdo (rango 0 a −1,3). El ángulo de endodesviación promedio previo a la aplicación de TB se encontró de 40,95 ± 8,6 DP sin corrección y de 22,3 ± 7,99 DP con corrección. Los principales efectos secundarios fueron: ptosis 14,2% (n = 3), diplopía 23,8% (n = 5) y desviaciones verticales 33% (n = 7).

Al año de seguimiento el 85,7% de pacientes tuvieron un resultado bueno con endotropía menor a 12 DP. Estos porcentajes disminuyeron a los 18 meses de seguimiento al 71,43%.

Conclusiones: El uso de TB tipo A permite obtener un resultado motor bueno a 18 meses en la mayoría de los pacientes. No se demostraron factores predictivos para el pronóstico.

© 2015 Sociedad Española de Oftalmología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

Partially accommodative esotropia (PAET) is of mixed origin, where the accommodative component does not entirely offset the deviation angle and leaves a significant residual attributed to a non-accommodative essential component.1

Mohney et al. affirmed that accommodative esotropia is the most prevalent form of ocular misalignment in Western populations, comprising 28% of strabismus cases in children and half of all endo-deviations.2 In Mexico, PAET is observed in 14% of all strabismus cases and is the third in order of frequency.3,4 Conventional treatment has consisted in prescribing total cycloplegic refraction and surgical correction of the residual deviation.

Injecting a botulin toxin (BT) in extraocular muscles is a technique that alters ocular alignment, producing temporary palsy and an overcorrection of strabismus which induces a shortening of the antagonist muscle. Histology demonstrates density changes in sarcomeres, which enhances permanent ocular alignment.5,6

Several authors have reported good results using BT for treating congenital esotropia, including Scott et al., Mc Neer and Gómez de Liaño et al.7 However, its use in PAET has only been reported in isolated cases.

The objective of this study was to determine the effectiveness of BT type A in transconjunctival injection applied to both median rectus in patients with PAET. Residual deviation was evaluated with the use of cycloplegic refraction as well as stability with 18 months follow-up.

Subjects, materials and method

A prospective, quasi-experimental analytical study comprising a cohort of patients with PAET diagnostic and use of total cycloplegic refraction at least 8 weeks prior to the application of BT in both median rectus for treating residual deviation in the Strabismus Department of the “Fundación Conde de Valenciana IAP” Ophthalmological Institute. Five U of BT were used for residual deviation greater than 18 DP and 2.5 U for residual deviation angles smaller than 18 DP. The treatment was applied under inhalatory general anesthesia in addition to topical anesthesia, using tetracaine in both eyes. After mechanical irritation at the application site, the treatment dose was injected through the trans-conjunctival intramuscular pathway without electromyographic signal guidance.

The study included patients with PAET diagnostic exhibiting residual deviation of 14 DP or greater regardless of gender and age, whose tutors agreed to participate in the study. The exclusion criteria comprised patients with muscular surgery history, irregular use of cycloplegic refraction or who declined informed consent.

The deviation was measured with the alternating screen maneuver and prisms, measuring distant visual capacity according to patient cooperation with the Snellen chart, HOTV or, with younger children, the Alan chart in logarithmic scale. All the patients underwent a complete ophthalmological exploration, including duction, version, refraction under cycloplegia using 1% cyclopentolate in children over 2 or 1% atropine in children below said age, anterior segment assessment and funduscopy.
Study variables comprised: (1) age; (2) sex; (3) visual capacity; (4) far and near angle deviation with and without correction prior to the application of BT and after the first week, 1, 3, 6, 12 and 18 months after the application; (5) hypermetropia grade; (6) AC/A ratio (gradient method); (7) accommodative factor\$^2; (8) presence of amblyopia; (9) response to treatment (successful: 0–6 DP, good: 7–12 DP, satisfactory: sum of successful and good; poor >12 DP). The data were collected in a Microsoft Office Excel 2010 database and analyzed with the PAWS version 18.0 statistical application. The results were divided on the basis of the follow-up time and descriptive statistics were performed. The agenda and amblyopia variables were considered categorical variables, whereas the remaining were considered continuous variables. The analysis included the association between continuous variables of interest, particularly those obtained at the end of the follow-up with those that could be considered as predictive factors, utilizing the ANOVE multivariate logistical regression analysis for continuous variables, Chi square for categorical variables and T for student for paired samples.

The study was submitted for evaluation by the Research and Ethics Committee of the "Fundación Conde de Valenciana IAP" Ophthalmological Institute and approved in accordance with the Helsinki declaration.

**Results**

Overall, the study comprised 21 patients who fulfilled the 18-month follow-up period. Of these, 33% (n=7) were males and 66.6% (n=14) females. Average visual capacity was of -0.28±0.25 logMAR for the right eye and -0.42±0.31 logMAR for the left one. PAET characteristics prior to treatment can be seen in Table 1. Amblyopia appeared in 33.3% of patients (n=7) with the following distribution: slight, 14.29% (n=3), moderate, 9.52% (n=2), severe 9.52% (n=2). All amblyopia patients were administered occlusion therapy when beginning the treatment, at a mean age of 7.35±2.46 years. The occlusion time ranged between 4 and 6 h per day according to age and amblyopia grade.

The endo-deviation angle, measured in far vision prior to the application of BT, was of 40.95±8.6 DP without correction and 22.3±7.99 with correction.

Overall, 19.05% of patients (4 patients) received a dose of 2.5 U of BT-A and 80.95% of patients (17) received 5 U of BT-A.

One week after application, with the use of far correction, 71.42% (n=15) exhibited exotropia with a mean of 31.33±22.45 DP, 14.29% (n=3) with mean esotropia of 6.66±5 DP and 14.29% (n=3) patients in ortho-position. In near vision, 66.6% (n=14) exhibited exotropia with a mean value of 32.84±23 DP, 14.29% (n=3) esotropia of 5.3±3.05 DP and 14.29% (n=3) ortho-position. These values were similar at application month one.

At application month 3, exotropia frequency diminished, with the majority of patients exhibiting both far and near esotropia with the use of correction (71.42%, n=15), 3 patients were in ortho-position (14.29%) and 3 persisted in esotropia (14.29%). One patient exhibited a poor response and it was decided to perform retro-insertion surgery for both medial rectus at follow-up month 6.

A los 6 months follow-up, with correction 14.29% (n=3) achieved ortho-position both far and near; 85.71% (n=18) of

**Table 1 – Characteristics of partially accommodative esotropia prior to treatment with botulin toxin type A.**

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset age (years)</td>
<td>2.31</td>
<td>1–5</td>
</tr>
<tr>
<td>Age of treatment (years)</td>
<td>6.43</td>
<td>2.12</td>
</tr>
<tr>
<td>Spherical equivalent</td>
<td>+4.86</td>
<td>+1.12 to +8.06</td>
</tr>
<tr>
<td>Hypermetropia diopeters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC/A</td>
<td>2.74/1</td>
<td>1.45 to 4.89/1</td>
</tr>
<tr>
<td>Accommodative factor</td>
<td>22.09</td>
<td>11–40</td>
</tr>
<tr>
<td>Pidriamatic diopeters</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Fig. 1 – Comparison between the far residual deviation average before botulin toxin application and after 12 and 18 months follow-up.](http://www.elsevier.es)
patients exhibited esotropia of 7.72 ± 4.01 DP average with far and 8.35 ± 4.82 DP with near. None of the patients exhibited exotropia.

After 12 months follow-up (19.05% n = 4) with correction continued in ortho-position and 80.95% (n = 17) persisted with esotropia with a mean value of 7.64 ± 4.59 DP, demonstrating diminished deviation against the baseline in a statistically significant manner (paired T for student; p < 0.01).

After 18 months follow-up, 4.7% were in ortho-position (n = 1) in far and near vision, 95.23% (n = 20) of patients were in far endotropia with a mean 9.05 ± 5.09 DP and near of 10.5 ± 5 DP with correction, with persistence of lower residual deviation (paired T for student, p < 0.01).

**Fig. 1** illustrates a comparison between the mean residual deviation in prismatic diopters prior to the application of BT, at 12 and 18 months after application. It can be seen that residual deviation is small at 12 months and is maintained at 18 months follow-up (p < 0.01).

The main observed side effects were: reversible ptosis, 14.2% (n = 3) with recovery in a mean time of 2–3 weeks; temporary diplopia, 23.8% (n = 5) and vertical deviation, 33% (n = 7). The presence of hyper–hypotrophy coincided with the development of ptosis, which were resolved one month after applying the treatment.

### Discussion

The utilization of BT type A as an option for treating PAET is a safe, accessible and low cost alternative. The age of presentation, the angle of endo-deviation measured with and without correction, and the percentage of patients with amblyopia in the present study match previous reports in the literature. The spherical equivalent was slightly above that reported in previous studies, reaching +4.93 DP. In contrast, AC/A was found to be 2.65/1, below the numbers reported in the literature, an average of 4.1/1.

It was observed that the response to treatment was poor only in 9.56% of patients at 6 months, with this percentage progressively increasing together with the follow-up period. At year one, 85.71% of patients exhibited satisfactory results (61.9% excellent and 23.81% good), although these percentages diminished to 71.43% at 18 months follow-up (42.86% excellent and 28.57% good).

The patients who exhibited better response during and at the end of the follow-up were those who at week 1 exhibited exotropia. This became statistically significant at follow-up month 12 (p = 0.016) but not at 18 months (p = 0.384) (Table 2).

#### Table 3 – Logistic regression analysis of baseline patient variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Response to treatment</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Value of p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>Excellent</td>
<td>1.86</td>
<td>±0.899</td>
<td>0.345</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>3</td>
<td>±1.414</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>2.5</td>
<td>±1.732</td>
<td></td>
</tr>
<tr>
<td>Age at treatment</td>
<td>Excellent</td>
<td>4.71</td>
<td>±1.976</td>
<td>0.077</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>8.2</td>
<td>±2.387</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>7.75</td>
<td>±3.775</td>
<td></td>
</tr>
<tr>
<td>Spherical Equivalent</td>
<td>Excellent</td>
<td>5.504</td>
<td>±1.134</td>
<td>0.242</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>3.534</td>
<td>±2.223</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>5.107</td>
<td>±2.652</td>
<td></td>
</tr>
<tr>
<td>AC/A ratio</td>
<td>Excellent</td>
<td>7.587</td>
<td>±3.627</td>
<td>0.554</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>2.926</td>
<td>±0.574</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>2.47</td>
<td>±0.887</td>
<td></td>
</tr>
<tr>
<td>Initial corrected far deviation</td>
<td>Excellent</td>
<td>18.14</td>
<td>±3.891</td>
<td>0.446</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>17.8</td>
<td>±4.494</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>22.25</td>
<td>±8.958</td>
<td></td>
</tr>
<tr>
<td>Accommodative factor</td>
<td>Excellent</td>
<td>30.43</td>
<td>±19.424</td>
<td>0.272</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>17.8</td>
<td>±6.834</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>19</td>
<td>±7.348</td>
<td></td>
</tr>
</tbody>
</table>
Table 4 – Response to treatment according to amblyopia level.

<table>
<thead>
<tr>
<th>Amblyopia</th>
<th>Excellent</th>
<th>Good</th>
<th>Poor</th>
<th>Value of p</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8 (57.1%)</td>
<td>4 (57.1%)</td>
<td>5 (71.4%)</td>
<td>0.653</td>
</tr>
<tr>
<td>Slight</td>
<td>1 (7.1%)</td>
<td>2 (28.6%)</td>
<td>1 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (14.3%)</td>
<td>1 (14.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>3 (21.4%)</td>
<td>0</td>
<td>1 (14.3%)</td>
<td></td>
</tr>
</tbody>
</table>

No relationship was found between the onset age (p = 0.345), treatment age (p = 0.077), spherical equivalent (p = 0.242), AC/A ratio (p = 0.554), initial deviation value (p = 0.446), accommodative factor (p = 0.272) or amblyopia (p = 0.653) with better response (Tables 3 and 4).

The visual capacity did not change at follow-up month 12 in both eyes (T for student, p > 0.05), although at month 18 visual capacity did improve (p < 0.05). The recovery time from adverse effect was 2–3 weeks, attributed to the dissemination of the drug at application. This matched reports found in the literature.1,12

BT is effective for treating residual deviation in PAET, maintaining stability in the deviation angle at 18 months follow-up with a single application. It has the advantage of not being expensive and its applicability in patients for whom surgery is contraindicated.

The use of BT type A in the early treatment of PAET allows excellent to good motor results in 71.43% of patients, similar to the reported values for non-accommodative esotropia.5 No prognostic predictive factor was demonstrated, although this could be due to the sample size which the authors regard as small.

Conflict of interests

No conflict of interests was declared by the authors.

References


