Botulinum toxin for strabismus correction

Uso da toxina botulínica para correção de estrabismo

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ABSTRACT

Purpose: *Evaluate the results and complications from type A botulinum toxin for strabismus treatment.* ***Methods:*** *Type A botulinum toxin (Prosigne®) was used in 20 patients from Faculdade de Medicina do ABC (FMABC) ophthalmology ambulatory from 2006 to 2009, for esotropia treatment. The application was performed in 15 children with esotropia smaller than 50 prism diopter (PD) in both medial rectus muscles, and in 5 adults with esotropia due to VI nerve paralysis or paresis, only in the opposite muscle. The incidence of adverse effects was also evaluated. The minimum post-treatment follow up was 3 months.* ***Results:*** *Three esotropic children were submitted to second application. Therefore, 18 applications were done. Of these, 14 were measured at least for six months of follow up. The average age at the time of application, in the children group, was 1.89(±0.54) years. Average convergent deviation before application was 36.67(±6.18) PD, after one week was -5.06(±23.05) PD and after three months was 17.50(±14.51) PD. At six months follow up, less than 10 PD of deviation was found in 50% (7/14) of the applications. The complications were blefaroptosis in 38.89% (7/18) applications, and vertical deviation in 11.11% (2/18). Seven applications in five adults were studied. In this group, average esotropic deviation before application was 46.43(±23.40) PD, after one week was 30.71(±30.61) PD and after three months was 41.20(±30.82) PD. Satisfied results was observed only in one patient from this group.* ***Conclusion:*** *Strabismus children got better with ocular deviation reduction after type A botulinum toxin (Prosigne®).*

Keywords: *Botulinum toxin type A/analysis; Botulinum toxin type A/therapeutic use; Strabismus/drug therapy; Similar drugs; Treatment outcome; Oculomotor muscles*

RESUMO

Objetivo: Verificar os efeitos da aplicação da toxina botulínica tipo A para o tratamento do estrabismo. **Métodos:** Realizou-se a aplicação de toxina botulínica tipo A (Prosigne®) em 20 pacientes acompanhados no ambulatório de oftalmologia da Faculdade de Medicina do ABC (FMABC), no período de 2006 a 2009, para o tratamento da esotropia. A aplicação foi realizada em 15 crianças com esotropias menores de 50 dioptrias prismáticas (PD) nos dois músculos retos mediais e em cinco adultos com esotropia secundária à paralisia ou paresia do VI nervo, somente no músculo antagonista ao acometido. A incidência de efeitos indesejáveis também foi avaliada. O tempo de seguimento mínimo foi de três meses. **Resultados:** Três crianças com esotropia foram submetidas a uma segunda aplicação, totalizando 18 aplicações. Destas, 14 aplicações realizaram no mínimo seis meses de acompanhamento. A idade média no momento da aplicação, no grupo das crianças foi de 1,89(±0,54) anos. O desvio convergente médio antes da aplicação foi de 36,67(±6,18) PD; após uma semana foi de -5,06(±23,05) PD, e após três meses foi de 17,50(±14,51) PD. Aos seis meses de acompanhamento cerca de 50% (7/14) das aplicações apresentaram desvio menor que 10 PD. As complicações apresentadas foram: blefaroptose em 38,89% (7/18) das aplicações e desvio vertical em 11,11% (2/18). Quanto aos pacientes adultos, foram realizadas sete aplicações em cinco pacientes. Neste grupo, o desvio esotrópico médio antes da aplicação foi de 46,43(±23,40) PD; após uma semana foi de 30,71(±30,61) PD; e após 3 meses foi de 41,20(±30,82) PD. Apenas um paciente com paresia apresentou satisfação com o resultado. **Conclusão:** Houve melhora do estrabismo com redução do desvio ocular nas crianças após aplicação da toxina botulínica tipo A (Prosigne®).

Descritores: Toxina botulínica tipo A/análise; Toxina botulínica tipo A/uso terapêutico; Estrabismo/quimioterapia; Medicamentos similares; Resultado de tratamento; Músculos oculomotores

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The authors declare no conflicts of interest

Received for publication: 7/11/2011 - Accepted for publication: 1/4/2013

Introduction

Congenital or infantile esotropia is a convergent non-accommodative persistent ocular deviation of relatively large angle which develops at approximately 6 months of age[1]. Among the different types of paralytic strabismus, sixth nerve palsy is the most frequent, followed by fourth and third nerve palsy. It leads to secondary phenomena such as a hyperfunction of the antagonist muscle and the contralateral conjugate muscle with compensatory head position[2]. There are several treatments for strabismus. Conservative options include prisms and orthoptic exercises; invasive treatments include surgery and botulinum toxin[3].

Botulinum toxin type A (BTA) has been studied since 1979 for selective weakening of extraocular muscles and it was rapidly incorporated into the treatment of strabismus as an alternative to traditional surgery[4-6].

Alan Scott[6] reports that alcohol was initially used to produce muscle weakness, while other researchers used various drugs such as neurotoxins and anaesthetics, but with inadequate effects. In 1981, Scott concluded that BTA was the ideal drug to cause temporary paralysis of extraocular muscles and produce permanent changes in ocular alignment with few side effects.

The drug acts on muscle nerve endings by blocking calcium transport. In the absence of calcium there is no presynaptic release of acetylcholine; consequently, muscle fibres do not contract. As the drug acts on nerve endings, not all muscle fibres of the motor unit lose their function concurrently. Its action is gradual and continuous, starting after approximately three days[6,7]. The paralysed muscle shows histopathological signs of myofibrillar atrophy and its terminal portion suffers demyelination, subsequently undergoing regeneration with the formation of new myoneural connections[8,9]. Once the muscle is paralysed its antagonist becomes stronger, thus changing eye position and alignment[3,7,9]. Maximum effect occurs 5-7 days after administration and can persist for a few weeks to 6 months depending on the dose[7,9,10]. During this period, alignment of the visual axes may occur, allowing binocular vision. Ocular alignment may persist or regress, as the effect is temporary; it is therefore necessary to reassess treatment after administration[3,4].

BTA is also used to treat spasms of facial muscles, entropion, corneal ulceration, and exposure keratitis[3,4,10]. For strabismus it is indicated in horizontal deviations under 50PD, acute third and fourth nerve palsy secondary to Graves' ophthalmopathy, residual or consecutive deviations after strabismus surgery, deviations secondary to retinal detachment surgery, and in patients unfit for general anaesthesia or surgical repair[8,10,11]. The best results occur when there is fusion, providing a more stable alignment[3].

Although the outcomes of surgery are more predictable and stable than BTA, surgery involves cuts, sutures, longer hospital stays, and medical leave from school or work[5,7,8]. The main advantage of BTA over surgery is administration under topical anaesthesia in adult patients or sedation in children, with little risk, lower cost, and no scars. Its disadvantages include transient ptosis and strabismus resulting from diffusion of the drug into surrounding muscles and, less frequently, scleral perforation, retrobulbar haemorrhage, and systemic effects[3,5,9,11].

The drug can be administered by direct visualisation, surgical exposure, or transconjunctival administration using electromyography to locate the target muscle[10,12]. Mendonça[12] published in 2005 an alternative technique that uses a forceps to guide the injection of the toxin, with results equivalent to electromyography but with a more delayed effect.

Although *Clostridium botulinum* produces various toxin types, type A is the most studied due to its sustained toxigenicity, ease of culture, and stable crystallisation[6]. Most studies on the subject consist of retrospective series using two types of BTA: Dysport™ (Speycool Pharmaceutics, UK) 500U, which contains albumin and lactose[13], and Botox™ (Allergan Inc., USA) 100U, which contains albumin and sodium chloride[14]. BTA Prosigne™ (CBTX-A, Lanzhou Biological Products Institute, China) 50 and 100U contains the excipients gelatine, dextran and sucrose, and there are no reports on its effect in strabismus — it has only been tested for dystonia and muscle spasms with good results[15-17].

The aim of this study was to assess the effects of botulinum toxin type A in the treatment of strabismus.

Methods

We studied 20 patients with esotropia treated with BTA Prosigne™ at the Ophthalmology Department of ABC Medical school from 2006 to 2009. Patients were divided into two groups: Group 1 included 15 children aged 1-3 years with comitant esotropia; Group 2 included five adults aged 24-52 years with sixth nerve palsy or paresis.

All patients underwent ophthalmic examination before and three months after administration of the toxin, with assessment of visual acuity, ocular motility, fundus examination, and static refraction. Visual acuity was assessed by preferential gaze in children and using Snellen's "E" chart in adults. The Krimsky method was used to measure deviation in young children and the prism cover test was used in adults. For statistical analysis, positive numbers were used to indicate esotropia and negative numbers for exotropia.

BTA was administered to children with esotropia under 50 PD and alternating fixation and adults with sixth nerve palsy starting less than a year earlier and good visual acuity.

Exclusion criteria were: patients with previous eye surgery, absence of visual perception, follow-up for less than three months, and other types of strabismus, such as vertical deviations, nystagmus, and dissociated vertical deviation (DVD).

The 100 IU Prosigne™ BTA was diluted in 2 ml of saline and applied after instillation of at least three drops of a topical anaesthetic agent (0.5% proparacaine hydrochloride). We used the technique described by Mendonça et al., using a Mendonça forceps to grasp the muscle body followed by toxin injection with a graduated syringe and a 26G needle[12].

All children and three adults were subjected to inhalation anaesthesia during administration. Two adults agreed to administration using only topical anaesthesia.

We used bilateral administration of 2.5 IU (0.05 ml) per medial rectus muscle in children and 5 IU (0.1 ml) in the antagonist muscle to that affected by the palsy, regardless of the degree of deviation, in adults.

A second administration of BTA or surgical correction was done after a minimum follow-up period of three months in patients with deviations greater than 10 PD after consulting patients or their guardians. Therapeutic success was defined as a deviation under 10 PD and/or patient satisfaction with the outcome.

The incidence of adverse effects such as ptosis and vertical deviation were also evaluated.

The minimum follow-up time was 3 months and the maximum was 1 year.

The study was approved by the Research Ethics Committee of ABC Medical School under number 002/2010, and patients or their guardians gave their informed consent.

SPSS (Statistical Package for Social Sciences) software version 17.0 was used for statistical analysis; a significance level of 5% (0.05) was adopted. The Friedman test was used to verify possible differences between time points in groups 1 and 2. When a statistically-significant difference was found, the Wilcoxon signed-rank test was used to identify which time points differed among themselves.

Results

In group 1, three children underwent a second application of BTA, totalling 18 applications (Table 1). Of these, 14 completed six months of follow-up. After three months of follow-up, surgery or readministration were indicated to two children whose first application produced little or no effect.

Mean age at the time of administration in group 1 was 1.89 (±0.54) years. The average deviation before administration was 36.67 (±6.18) PD of esotropia; one week after administration it was -5.06 (±23.05) PD; and after three months it was 17.50 (±14.51) PD (Table 2). Since a statistically-significant difference was found when comparing the three time points concurrently, the Wilcoxon signed-rank test was used to identify which time points differed among themselves pairwise, and significant differences was found in all comparisons. At three months, 61% (11/18) of patients had a deviation under 10 PD. Complications included ptosis in 38.89% (7/18) of cases and vertical deviation in 11.11% (2/18), with complete regression after a month.

After six months of follow-up 50% (7/14) of patients had a deviation under 10 PD, but there were still differences in esotropia when comparing the four time points concurrently and pairwise (Tables 3 and 4). Four patients in this group were indicated readministration but only 3 actually received it, and therapeutic success was achieved in 2 of them.

In group 2, two adults underwent readministration after three months of follow-up, totalling 7 applications. The causes of sixth nerve impairment were: neurosurgery (one patient), trauma (two patients), neurotoxoplasmosis (one patient) and Guillain-Barret syndrome (one patient) (Table 5). Among adult patients, the average age at administration was 37.40 (±9.93) years and the mean time from the onset of the palsy until administration was 9.14 (±5.08) months. The average deviation

Table 1

Results of application of botulinum toxin type A (Prosigne™) in group 1.

Apl	Pac	S	Age (years)	Pré-apl (PD)	1 week (PD)	3 months (PD)	6 months (PD)	Result	Adverso effect
1	1	M	2,5	35	-20	25	25	Readm	Ptosis
2	1*	M	2,91	30	-30	10	10	Good	Ht
3	2	M	1,75	40	40	40	x	Surgery	
4	3	F	1,66	40	-30	0	0	Good	
5	4	M	1,66	30	0	20	30	Surgery	
6	5	M	2,08	30	10	30	x	Readm	Ptosis/Ht
7	6	F	1,58	40	20	25	25	Readm	Ptosis
8	6*	F	2,66	30	10	30	30	Surgery	
9	7	F	1,91	45	-30	10	10	Good	Ptosis
10	8	F	1,33	45	-20	5	40	Readm	Ht
11	8*	F	2,25	40	-5	0	x	Good	Ptosis
12	9	F	1,50	40	-5	-5	-5	Good	
13	10	M	2,33	45	0	10	10	Good	
14	11	M	1,25	45	35	40	40	Surgery	
15	12	F	1,08	30	-40	5	5	Good	Ptosis
16	13	M	1,16	30	4	4	30	Readm	
17	14	M	2,08	35	0	4	4	Good	
18	15	M	2,41	30	-30	0	x	Good	

Apl: application; Pac: patient; S: sex; Pre-apl: pre-application; PD: prism dioptre; Readm: readministration; Ht: hypertropia. *Patients submitted to readministration.

Table 2

Ocular deviation in cases followed-up for at least 3 months in Group 1.

Variable	N	Mean	Standard deviation	Significance(p)
Pré-aplicação	18	36,67	6,18	
1 semana	18	-5,06	23,05	<0,001
3 meses	18	14,06	14,36	

Table 3

Ocular deviation in cases followed-up for at least 6 months in Group 1.

Variable	N	Mean	Standard deviation	Significance(p)
Pré-aplicação	14	37,14	6,42	
1 semana	14	-7,57	21,60	<0,001
3 meses	14	13,07	12,91	
6 meses	14	20,00	13,87	

Table 4

Pairwise comparison of ocular deviation between time points in cases followed up for at least 6 months in Group 1.

Pair of variables	Significance (p)
1 week – pre-application	<0,001
3 months – pre-application	<0,001
6 months – pre-application	0,003
3 months – 1 week	<0,001
6 months – 1 week	0,001
6 months – 3 months	0,042

Table 5

Results of application of botulinum toxin type A (Prosigne™) in group 2.

Apl	Pac	Age (years)	Pre-apl (PD)	1 week (PD)	1 month (PD)	3 months (PD)	Cause	Time (months)
1	1	24,25	40	20	35	45	surgery	4
2	1*	25	45	30	35	35	surgery	9
3	2	51,58	40	40	40	40	trauma	5
4	3	38,16	90	90	90	90	neurotox	16
5	4	42,58	60	0	30	35	trauma	5
6	4*	43,33	35	35	30	30	trauma	9
7	5	38,66	15	0	0	6	G. Barret	16
		37,40	**46,43**	**30,71**	**37,14**	**40,14**		**9,86**

Apl: application; Pac: patient; Pre-apl: pre-application; PD: prism dioptre; G.Barret: Guillain-Barret syndrome. *Patients submitted to readministration.

before administration was 46.43 (±23.40) PD of esotropia; one week after administration it was 30.71 (±30.61) PD; and after three months it was 41.20 (±30.82) PD. Patients then underwent surgery, except for the patient with paresis since their esotropia had decreased to 6 PD and the patient was satisfied with the outcome.

Discussion

Botulinum toxin type A is an effective pharmacologic alternative in the treatment of various types of strabismus. In infantile esotropia, simultaneous bilateral administration in the medial rectus muscles can provide stable ocular alignment with negligible risk. More than one application may be required in 50% of patients[8]; McNeer et al.[18] report up to four applications. In our study the maximum number of applications was two, when the patient or guardian opted for a second application. Each application is independent and there is no cumulative effect, however Abbasoglu et al.[5] report that secondary injections have a greater effect than the first application.

The effect is also related to the patient's age. In young patients there are no muscular mechanisms opposing changes in the original deviation, as described by Campos et al.[19]. The lack of suppression can also be a good prognostic factor for restoration of binocular vision using prisms, surgery, or BTA[20]. These factors account for the better outcomes found in children.

In our study, complications (ptosis in 38.89% and vertical strabismus in 11.11%) were transient and consistent with the literature. No systemic effects were observed, which is also consistent with the literature. The American Academy of Ophthalmology[10] reported an incidence of 17-50% for temporary ptosis and 17% for hipertropias. Treatment success rates decreased from 61% to 50% from the third to the six month of follow-up after application. These data are consistent with the literature, despite the difficulty in comparing results. In a study by the American Academy of Ophthalmology[10], the percentage of patients achieving a deviation equal or less than 10 PD was 33-72%, depending on the type of strabismus. Allan Scott[6] in his pioneering work found good results in about 40% of patients with only one application. In a study by Cronemberger et al.[11], 80.9% of patients achieved deviations under 10 SD, decreasing to 53% after two years.

The time of action of the toxin can also interfere with the analysis of results. Abbasoglu et al.[5] consider that results are affected by factors inherent to optical correction, secondary deviations, and amblyopia, among others, which can reduce the rates of therapeutic success in longer follow-up periods. However, Cronemberger et al.[11] reported that muscle weakening can last from 2 weeks to 8 months with permanent change of ocular alignment depending on the concentrations of the injected drug. Therefore, a study with a more prolonged follow-up period may yield different results.

Another factor that complicates comparisons is that our study was the only one that used a botulinum toxin of Chinese origin for the treatment of esotropia. There are great variations in the literature with regard to treatment types, doses, and types of botulinum toxin[4,5,7,11,12].

In 2000, Tang & Wan[17] compared the results of treatment with Botox™ and Prosigne™ for facial dystonia and concluded that the former cost 8-10 times more than the latter and the dose

of the Chinese drug needed to produce similar results was higher, probably due to differences in the purification process of the two formulations. However, no differences were found in their adverse effects. In a double-blind study by Rieder et al.[16] on facial dystonia, a dose ratio of 1:1.5 was reported for Botox™ and Prosigne™, respectively, with no differences in efficacy and safety. Therefore, the results of our study may have been influenced by the low administered dose, and higher doses might produce better results[18,19].

Even though BTA produces good results in acute sixth nerve palsy[7,9-11], in our study there was no improvement in deviation, except in the patient with muscle paresis. The results were probably influenced by the administered dose, the delay in seeking ophthalmic care (9.89 months), and the level of muscle activity in the paralysed muscle.

In conclusion, an improvement in strabismus with reduced ocular deviation was found in children after application of botulinum toxin type A (Prosigne™).

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