Botulinum A Toxin Therapy on Esotropia in Children

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Abstract

A prospective descriptive study was conducted to determine the results of Botulinum Toxin Type A (BTA) injection on esotropia in children, as this may be an alternative to incisional surgery for strabismus. Between September 1998 and February 2002, eleven patients (6 boys and 5 girls) with esotropia were treated with BTA at the Department of Ophthalmology, Songklanagarin Hospital. The average ages at the time of the first and second treatments were 26.8 months (range 14-40 months) and 32.3 months (range 19-54 months), respectively. An open sky procedure was used to inject the BTA. Alignment within ± 10 prism of orthotropia was considered a successful outcome of BTA treatment in the patients. If the result of the first injection was an incomplete paralysis and the strabismus remained undercorrected, the subsequent dose was increased up to double the initial dose. The mean deviation angle was 40.4 prism diopter (PD) before the first injection and 24.5PD before the second injection. Eight of 11 (72.7%) cases had a sucessful outcome. BTA injection in childhood esotropia may be an alternative to incisional strabismus surgery.

Key word : Esotropia, Botulinum A Toxin, Children

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Esotropia in children is a relatively common condition which usually develops around the second or third month of life in the early onset group and after 6 months in the late onset group. The majority of children are neurologically and developmentally normal. The esotropia is presumed to develop because of a failure of maturation of motion processing, and other features such as latent nystagmus, dissociated

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deviation, oblique muscle dysfunction and lack of binocular connectivity in the primary visual cortex[1].

The usual treatment is a combination of orthoptic and surgical management that can achieve satisfactory alignment of the eyes with peripheral sensory fusion but no stereopsis. Theoretically, relatively early surgical alignment may result in better quality of binocular function, although this possibility has never been rigorously tested. There are disadvantages in operating too early. The surgery is technically more difficult and, since the posterior segment of the eye in infancy is relatively underdeveloped, a standard medial rectus recession in the first few months of life can result in reduced eye movement later on[2]. Hiles et al[3] studied children under the age of one who underwent surgical alignment; the eyes of only 31 per cent of them were aligned with initial bimedial rectus recessions alone.

Congenital esotropia is functionally curable if treated early. Botulinum toxin treatment is attractive in that it avoids incisional surgery and its complications. Botulinum Toxin Type A (BTA) is a large protein molecule produced by Clostridium botulinum which can be crystallized in a stable form. BTA blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals; it enters the terminals and inhibits the release of acetylcholine. It produces a localized chemical denervation muscle paralysis.

This article reports the use of BTA injection as a potential alternative to incisional strabismus surgery in the treatment of childhood esotropia. The research was approved by the Ethics Committee, Faculty of Medicine, Prince of Songkla University.

MATERIAL AND METHOD

Between September 1998 and February 2002, 11 patients (6 boys and 5 girls) younger than 5 years with esotropia were treated with BTA (Botox; Allergan, Irvine, CA) at the Department of Ophthalmology, Songklanagarin Hospital. The exclusion criteria were central nervous system disorders, amblyopia, retinal disease and previous eye surgery.

Information concerning the study and possible complications was given to the parents in oral and written form prior to their giving consent. Before treatment, the angle of deviation was measured with the alternate prism cover test or Kimsky light reflex method twice within a month, it ranged from 14 to 60 prism diopter (PD) with alternated fixation. The visual acuity test was measured with the Teller test or Cardiff card, depending on the patient. The angle of deviation and visual acuity were tested by an orthoptist. Complete ophthalmologic evaluations were carried out; these included examination of the fundus, extraocular eye movement (duction and version), oblique muscle overaction, dissociated vertical deviation (DVD), nystagmus, palpebral fissure and the refraction (1% Cyclogly). Photographic records were done for all patients.

An open sky procedure was used to inject BTA. All patients were injected in an operating room under general anesthesia. After the anesthesia was induced, each patient underwent simultaneous bilateral injection of BTA into the medial rectus muscle under direct visualization by an ophthalmologist. The fornix approach was done before BTA was injected into the medial rectus muscle. A 30-gauge needle was advanced along the course of the muscle approximately 10 mm from the muscle insertion. The guideline for the initial dosage was based on the degree of deviation and body weight as advised by Scott et al[4] (Table 1).

Follow-up assessments were made at weekly intervals for 4 weeks, and monthly thereafter for at least 6 months. If the result of the first injection was an incomplete paralysis and the strabismus remained undercorrected (esotropia more than 10 PD for longer than 4 weeks), the subsequent dose was increased up to double the initial dose. The dosage was increased to a maximum of 5 U. Alignment within $\pm$ 10 prism of orthotropia was considered a sucessful outcome of BTA treatment.

Data were abnormally distributed, so the angle deviation during the first and second injections

Table 1. Botulinum toxin dosage, strabismus.

	Body weight			
	>12.5 kg	10-12.5 kg	6-9 kg	<6 kg
Horizontal or vertical deviations <20 PD	1.25 U	1.25 U	1.25 U	-
Horizontal or vertical deviations 20-50 PD	1.25-2.5 U	1.25-1.75 U	1.25 U	1.0 U

were compared by the Wilcoxon signed-rank test. For all inferential statistics, p-values less than 0.05 were considered significant.

RESULTS

Eleven patients (6 boys and 5 girls) with esotropia were treated with BTA. No one had anisometropia or an abnormal eye examination (except esotropia). One patient had a family history of strabismus. These data are summarized in Table 2. The average ages of the patients at the time of the first and second treatment were 26.8 months (range:14-40 months) and 32.3 months (range: 19-54 months), respectively. The mean deviation angle was 40.4 PD before the first injection and 24.5 PD before the second injection (Table 3). Nine of 11 patients (81.8%) needed a second injection. Fig. 1 to 3 show the effectiveness of treatment. The mean length of follow-up after the last injection was 10.3 months (range: 4-27 months). Eight of the 11(72.7%) children maintained the successful outcome, while three of them (27.3%) did not (Fig. 4). In the three unsuccessful cases, the angle of deviation had decreased about 14.3 per cent (case 2), 12.5 per cent (case 3) and 50 per cent (case 5), as shown in Fig. 5. Early adverse results of the BTA injections were subconjunctival hemorrhage (12.5%), and ptosis (12.5%), which disappeared within a month. Exotropia occurred in 15 (75%) of the injections, peaked at 1.7 weeks (range: 1-4 weeks) and disappeared within 4 months. Amblyopia was detected after three of the 11(27.3%) injections, but was not related to ptosis. All but one of these patients responded to occlusion treatment. One patient (case 2) did not respond to treatment because of non-compliance to eye occlusion. DVD and inferior oblique overaction (IOOA) were found in case 1 and 2, respectively. Nystagmus, globe perforation or systemic complications were not encountered.

DISCUSSION

In 1973, Scott[5] reported that BTA was effective in treating extraocular paralysis in animals and introduced the use of BTA in cases of acute paralytic strabismus in 1978. In 1981, he reported the use of BTA injections into the extraocular muscles as an effective alternative to conventional surgery in the treatment of strabismus in adults[6]. Then, in 1990, he reported the results of BTA injections into the extraocular muscles of children[4]. These had a success rate (orthophoria ± 10 PD) of 33.3 per cent-89 per cent[4,7-10]. Biglan et al[9] found that in 66 per cent of cases there was a return to an unacceptable deviation that required strabismus surgery. In the present study, the success rates at 6 months after the first and second treaments were 27.3 per cent and 77.8 per cent, respectively (Fig. 3). After the first injection, the authors found the failure rate highest in the first 3 to 6 months. After that the rate slowly decreased. At this time, 8 of 11 (72.7%) showed a successful outcome while the others showed a decrease of the angle of esotropia. The authors suggested surgery for one patient but the parent refused because she prefered a 30 prism esotropia. The other patient still needs amblyopia treatment.

Table 2. Characteristics of patients.

Patient	Sex	Age at onset (wk)	Refraction sphere/cylinder/axis	
			Right eye	Left eye
1	Male	8	2.25/0.25/70	2.25/0/0
2	Male	2	0/0.5/90	0/0.5/90
3	Male	20	2.25/0.5/180	2.62/0/0
4	Female	Birth	0.75/1.0/90	0.75/1.0/90
5	Male	104	0.25/0.5/120	0.25/0.5/100
6	Female	8	0.25/0.25/180	0.25/0.25/180
7*	Female	52	0/0.50/140	0/0.25/140
8	Male	Birth	2.0/0.5/110	2/0/0
9	Female	24	0/0.12/90	0/0.25/10
10	Female	40	-1.75/1.5/180	0/0/0
11	Male	16	0/0.25/90	0.65/0/0

* Only patient with family history of strabismus

Table 3. The results of BTA injection.

Cases	No of injections (mos)	Age at treatment (prism)	Preinjected deviation (wks)	Maximum angle change (prism)	Postinjected deviation	Duration on ortho (mo)
1	1	24	Esotropia 45	Exotropia 45 (1)	Esotropia 35	10
1.2*	2	37	Esotropia 35	Exotropia 70 (2)	Ortho	9 1/2
2	1	28	Esotropia 35	Esotropia 16 (1)	Esotropia 18	0
2.2*	2	29	Esotropia 18	Exotropia 10 (2)	Esotropia 30	4
3	1	14	Esotropia 40	Exotropia 25 (4)	Esotropia 25	4
3.2*	2	23	Esotropia 25	Exotropia 40 (3)	Esotropia 10	20
4	1	43	Esotropia 30	Exotropia 35 (2)	Esotropia 6	25
5	1	52	Esotropia 60	Exotropia 30 (1)	Esotropia 20	0
5.2*	2	54	Esotropia 20	Exotropia 55 (2)	Esotropia 30	7
6	1	33	Esotropia 50	Exotropia 25 (1)	Esotropia 20	3
6.2*	2	40	Esotropia 20	Exotropia 25 (3)	Ortho	2
7	1	53	Esotropia 14	Exotropia 80 (2)	Esotropia 10	17
8	1	40	Esotropia 50	Exotropia 50 (2)	Esotropia 18	2
8.2*	2	48	Esotropia 18	Exotropia 90 (1)	Esotropia 6	7 1/2
9	1	17	Esotropia 60	Ortho (1)	Esotropia 30	1
9.2*	2	22	Esotropia 30	Exotropia 60 (2)	Ortho	8
10	1	14	Esotropia 30	Ortho (1)	Esotropia 30	1
10.2*	2	19	Esotropia 30	Exotropia 35 (1)	Ortho	4
11	1	16	Esotropia 30	Ortho (1)	Esotropia 25	1
11.2*	2	19	Esotropia 25	Exotropia 30 (1)	Ortho	5 1/2

* second injection

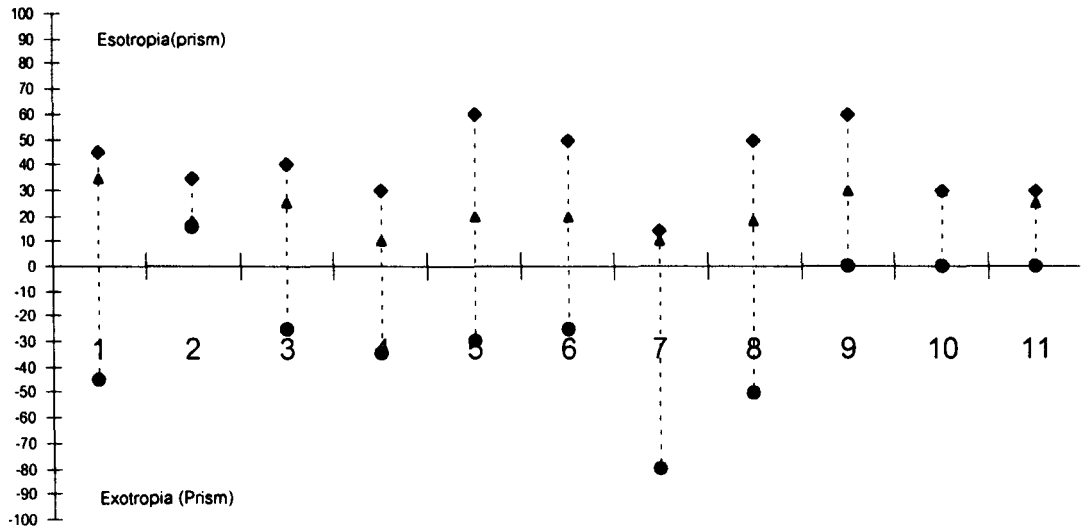

Fig. 1. First preinjection deviation (diamond), the maximum change in alignment achieved after BTA injection (circles) and the final result (triangles).

Campos et al[10] reported that bilateral simultaneous BTA injections into the medial rectus muscle are most effective in patients younger than 7 months. In the present study the authors included only children older than 7 months, so it is difficult to make a useful comparision between the two studies.

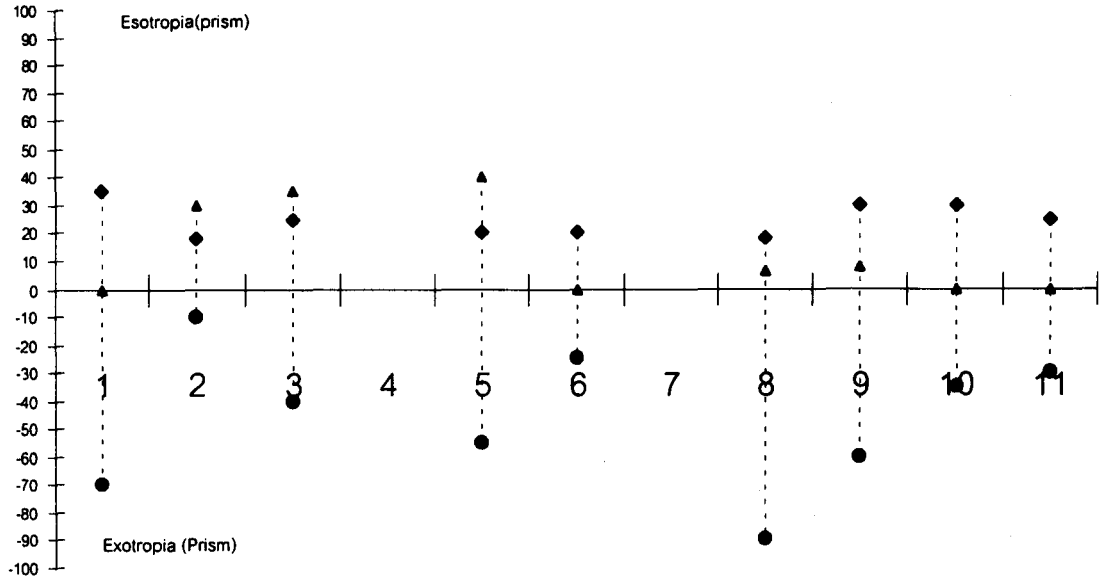

Fig. 2. Second preinjection deviation (diamond), the maximum change in alignment achieved after BTA injection (circles) and the final deviation (triangles).

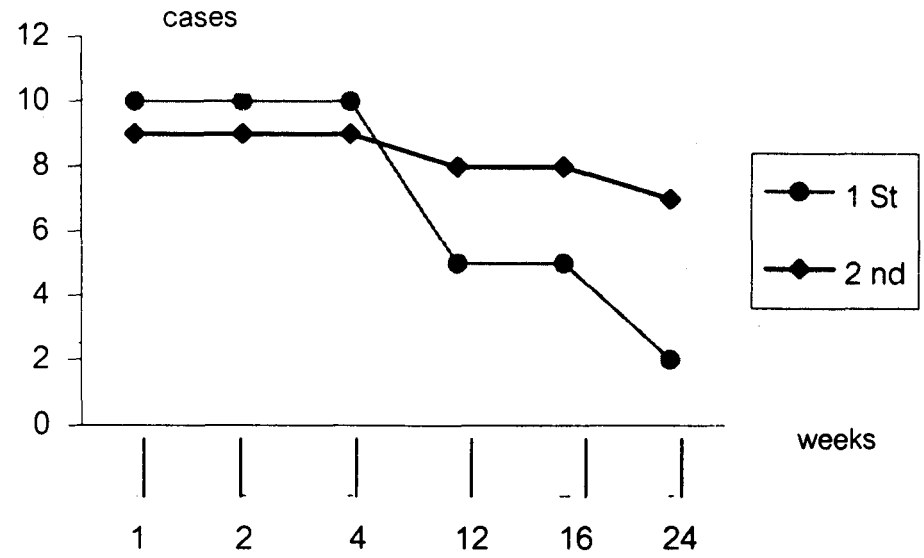

Fig. 3. Diseases free of esotropia after first injection (circles) in 11 cases and the second injection (diamond) in 9 cases.

For number of injections and dose of BTA, Abbasoglu et al[11], in their study in adults, found no association between the number of injections and outcome. However, Scott et al[4] found that the alignment results of a second injection were better than those of the primary injection. In the present study, it was found that the second injection had a greater clinical effect than the primary injection at 6 months, but the number of children included in the study was too small for a meaningful statistical analysis. Furthe-

Fig. 4. Case 4, who had esotropia and had a sucessful outcome at pre BTA injection (A), post BTA injection 13 months (B), and the final result (C).

Fig. 5. Case 5, who had esotropia and needed the second BTA injection at pre the first BTA injection (A), and pre the second BTA injection (B), and the final result (C).

more, the follow-up time after the second injection was not long enough to guage its effect.

The advantages of BTA injections are avoidance of incisional surgery and its complications, especially in small children, and the absence of persistent histological changes in muscle fibers[12]. From the authors' experience only a mild conjunctival scar was found but no fibrosis at the time of the second injection.

The disadvantages of the BTA injection include the need for multiple injections; an initial overcorrection; an unstable alignment change; BTA induced paralytic strabismus occurring a month or two after the injection; transient partial ptosis; transient vertical strabismus; and globe perforation[13, 14]. Magoon et al[14] reported that re-injection was necessary in 85 per cent of patients. This is similar to the present finding of 81.8 per cent needing a second injection. Exotropia after the first injection occurred less frequently than after the second injection, the difference being statistically significant at 2 weeks after the injection. Early complications were subconjunctival hemorrhage and ptosis, whereas late complications were amblyopia, IOOA and DVD. The authors used an open sky procedure, which prevented globe perforation. There were no systemic complications. McNeer et al[8] found DVD in 24 per cent of cases and IOOA in 29 per cent These figures are slightly higher than in the present study with DVD occurring in one of the patients and IOOA in two. None required surgery. The incidence of secondary vertical anomalies was relatively small. This may be because the authors have not yet followed-up the cases for a sufficient length of time (such follow-up will be arranged).

Magoon[15] reported that the results of BTA injection were similar after shorter and longer follow-up periods. He suggested that BTA produces a 2 to 5 year stable improvement for strabismic children, so long-term follow-up and evaluation of fusion ability are recommended.

There are many published data on BTA in the treatment of childhood strabismus from Europe and South America[16]. Unfortunately, in South East Asia there are few such reports and these are confined to adults[17] and cases of cranial nerve palsy. Even though the present pilot study involved only a small number of cases and short-term follow-up, BTA appears to be an effective drug for treating esotropia in children.

SUMMARY

BTA injections in childhood esotropia should be considered as an alternative to incisional strabismus surgery.

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สารชีวพิษโบทูลินัม เอ รักษาตาเขเข้าในในเด็ก

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การศึกษาแบบ prospective เพื่อวิเคราะห์ผลการฉีด botulinum toxin type A (BTA) ในเด็กตาเขเข้าในว่าเป็นทางเลือกหนึ่งในการรักษาแทนการผ่าตัดได้หรือไม่ ข้อมูลเก็บตั้งแต่ เดือนกันยายน 2541 ถึง เดือนกุมภาพันธ์ 2544 ผู้ป่วยจำนวน 11 คนเป็นชาย 6 คนเป็นหญิง 5 คน ทุกคนมีปัญหาตาเขเข้าใน ที่ได้รับการรักษาโดยการฉีด botulinum toxin type A (BTA) ในแผนกจักษุ โรงพยาบาลสงขลานครินทร์ ผู้ป่วยมีอายุเฉลี่ย 26.8 เดือน (พิสัย 14–40 เดือน) และ 32.3 เดือน (พิสัย 19–54 เดือน) เมื่อได้รับการรักษาครั้งที่ 1 และครั้งที่ 2 ตามลำดับ การฉีดยาได้ฉีดหลังจากมีการเปิดเยื่อบุตาขาวออกซึ่งเรียกว่า "open sky procedure" ผลการรักษาผู้ที่มีตาตรงหรือเขในมุม ± 10 ปริซึ่มจะถือว่ามีความสำเร็จของการรักษา ส่วนผู้ที่ยังมีตาเขเข้าในมากกว่า 10 ปริซึ่มจะได้ฉีด BTA ซ้ำโดยเพิ่มขนาดยาขึ้นอีก 1 เท่าของการฉีดครั้งแรก ก่อนการรักษาครั้งที่ 1 และครั้งที่ 2 ตรวจพบค่าเฉลี่ยของมุมเขเข้าใน 40.4 ปริซึ่มและ 24.5 ปริซึ่ม จนกระทั่งมีการรายงาน ผู้ป่วย 8 ใน 11 คน (ร้อยละ 72.7) ยังมีผลการรักษาดีอยู่ โดยสรุปแล้วการฉีด BTA อาจจะเป็นทางเลือกหนึ่งสำหรับการรักษาอาการตาเขเข้าในในเด็ก

คำสำคัญ : ตาเขเข้าใน, สารชีวพิษโบทูลินัม เอ, เด็ก

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