FACTORS INFLUENCING SUCCESS AND DOSE–EFFECT RELATION OF BOTULINUM A TREATMENT

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SUMMARY

Botulinum toxin type A (BTA) treatment is an alternative to strabismus surgery. In this retrospective study the data on 45 esotropic and 49 exotropic patients with concomitant strabismus who were treated with BTA were analysed for dose–effect relationship, the effect of repeat doses and amblyopia on success of botulinum treatment. The esotropic patients were treated with a total of 80 and exotropic patients with 91 injections. The deviations were corrected within 5 degrees of straight in 33% of esotropic and 18% of exotropic patients. In esotropic patients the effect was dose dependent. This relation was not shown in exotropic patients. The repeat doses of BTA corrected the deviation to the same extent as the primary ones for both esotropic and exotropic patients.

Botulinum toxin type A (BTA) treatment is an alternative to traditional strabismus surgery. It can provide a temporary weakness of an overactive or tight muscle that permits the relaxed muscle to be stretched by the unopposed antagonist. The long-term muscle lengthening improves the ocular alignment.[1]

BTA treatment has the advantage over surgery in that it is easily administered in the outpatient clinic with the use of only topical anaesthesia and causes little or no post-injection discomfort. Possibly the most important disadvantage of BTA treatment, apart from its commonly encountered paralytic effects, is that it produces effects that are not as predictable and stable as traditional surgery. In this study we analysed our data to investigate the dose–effect relationshp and the effect of repeat doses.

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MATERIALS AND METHODS

In this retrospective study case notes of patients with concomitant horizontal deviations treated with BTA injections at Hacettepe University between 1984 and 1994 were reviewed. Many of our patients came from a distance. Hence to evaluate our results we fixed a period of time within which all our patients had follow-ups and excluded those having their first follow-ups later than this time period. The inclusion criteria required a follow-up period of 4 months with successive measurements indicating the angle of strabismus was stable. We included those patients having 2–3 months of follow-up only if there was full recovery from the paralytic effects of BTA such as ptosis and eye movement restrictions. Ninety-four patients with horizontal concomitant strabismus who satisfied the criteria were included in the study.

All patients had a complete ophthalmological evaluation including measurement of visual acuity, refraction, biomicroscopy and fundus examination. None of the patients had restriction of ocular rotation. The angles of deviation at distance in the primary position were measured with a prism cover–uncover test or synoptophor with full optical correction. The Krimsky method was used for those patients who were unable to fixate due to low visual acuity. Measurements in prism dioptres were converted to degrees for data analysis. Angles of deviation were denoted by positive numbers for esotropic patients and negative numbers for exotropic patients.

The BTA injections were given after written consent had been obtained. Before the procedure topical cocaine was applied into the conjunctival sac for anaesthesia. Injections were performed under electromyographic control with monopolar needles. All patients were evaluated and given BTA treatment by one of the authors (A.S.S.). We used British botulinum toxin (Dysport; *Clostridium botulinum*

Table I. The distribution of esotropic patients with regard to BTA dose and number of repeat doses applied

BTA dose (units)	Injection 1	Injection 2	Injection 3	Injection 4	Total
1.25	1	—	—	—	1
2.5	16	13	7	1	37
5	10	2	1	—	13
7.5	—	1	1	—	2
10	7	2	1	—	10
15	7	2	1	—	10
20	5	3	—	—	8
Total	45	23	11	1	80

type A toxin haemagglutin, Porton Products, UK). The BTA was diluted so that regardless of the dose a bolus of 0.1 ml could be injected. The dose applied ranged from 2.5 to 20 units. This retrospective study covers a 10 year period. Initially 2.5 units of BTA were injected into each patient regardless of the angle of deviation. Upon realising that the improvements in deviation were not satisfactory, the BTA dose applied was increased to 5 and then to 10, 15 and 20 units. We did not set up a range of deviations for which we would apply a specific BTA dose; the decision for re-injection was given if the post-treatment deviation was greater than 5° of straight after a follow-up period of 6 months. Some patients who were satisfied with their appearance refused to have a repeat injection.

The esotropic and exotropic patients were evaluated separately. Two methods were used to evaluate the effect of BTA in strabismus.[1] The first was to calculate the percentage reduction in the pre-treatment deviation after the paralytic effect disappeared, using the following formula:

$$\frac{\text{Pre-treatment deviation} - \text{Post-treatment deviation}}{\text{Pre-treatment deviation}} \times 100$$

The second method was to determine whether the post-treatment deviation was within 5° of straight. Those patients having a post-treatment deviation within 10 degrees of straight were evaluated as cosmetically successful. The esotropic and exotropic patients were grouped according to the dose of BTA applied and the number of injections performed.

We investigated the effect of repeat doses on the percentage reduction of the initial deviation (provided that the same toxin dose was used) to find out whether there is any cumulative effect of BTA. Secondly we looked for the effect of a change in BTA dose on the percentage reduction of the initial deviation. Thirdly, we investigated the effect of the initial deviation on having a post-treatment deviation within 5 and 10 degrees of straight. Patients were divided into four groups according to their pre-treatment deviations: group I, 5–10 degrees; group II, 11–15 degrees; group III, 16–25 degrees; group IV, >25 degrees.

We also evaluated the incidence of ptosis with respect to increments in BTA doses. This is the most common paralytic side effect of BTA treatment.

RESULTS

Forty-five esotropic patients aged 15–55 years (24 ± 0.8 years) were included in the study. Eleven patients had had previous strabismus surgery once and 1 patient twice; the rest were primary esotropes. The mean pre-treatment deviation was 17.6 ± 0.8 degrees (range 5–45 degrees). A total of 80 BTA injections were performed with a mean of 1.7 per patient. Mean post-treatment deviation was 10.1 ± 1.5 degrees (range 0–26 degrees) with an average improvement of 8.0 ± 1.6 degrees (range 0–42 degrees).

Forty-nine exotropic patients aged between 13 and 57 years (mean 24.8 ± 0.8 years) enrolled in the study. Fifteen exotropic patients had had previous strabismus surgery and 4 of them had consecutive exotropia. Three patients had had strabismus surgery twice and 1 patient three times; all had consecutive exotropia. Five patients had secondary exotropia. The remaining patients had primary exotropia. The mean pre-treatment deviation was −15.9 ± 0.8 degrees (range −5 to −45 degrees). A total of 91 injections were applied with an average of 1.8 injections per patient. The mean post-treatment deviation was −9.9 ± 1.3 degrees (range 0 to −35

Table II. The distribution of exotropic patients with regard to BTA dose and number of repeat doses applied

BTA dose (units)	Injection 1	Injection 2	Injection 3	Injection 4	Injection 5	Injection 6	Total
1.25	1	—	—	—	—	—	1
2.5	15	6	5	1	—	—	27
3.75	1	—	—	—	—	—	1
5	11	7	4	4	1	1	28
7.5	2	—	—	—	—	—	2
10	9	4	2	2	—	—	17
15	6	1	3	1	—	—	11
20	4	—	—	—	—	—	4
Total	49	18	14	8	1	1	91

Table III. The mean pre-treatment and post-treatment deviations, mean improvement and percentage reduction in initial deviations (± standard errors) for esotropic patients (min.–max.)

Injection no.	BTA dose (units)	Pre-treatment deviation (degrees)	Post-treatment deviation (degrees)	Mean improvement (degrees)	Correction (%)
1	2.5	20.2 ± 1.9 (8.35)	10.4 ± 1.8 (0–25)	9.9 ± 1.9 (0–25)	40.3 ± 7.3
2	2.5	13.5 ± 1.8 (4–25)	12.6 ± 1.8 (3–26)	2.9 ± 1.1 (0–15)	18.5 ± 5.4
3	2.5	14.7 ± 2.4 (6–26)	11.3 ± 2.7 (5–24)	4.0 ± 1.7 (0–13)	26.1 ± 10.3

degrees) with a mean improvement of 4.7 ± 0.8 degrees (range 0–20 degrees).

The distribution of esotropic and exotropic patients receiving BTA treatment according to dose applied is shown in Tables I and II. As there were few patients receiving 1.25 u, 3.75 u or 7.5 u BTA they were excluded from the study.

We first evaluated the effect of repeat dose applications on the percentage reduction in the initial deviation when the toxin dose was kept constant. For this purpose the largest patient group, which received 2.5 u BTA, was selected. Sixteen esotropic patients had a 2.5 u BTA injection at the first application, 13 at the second, 7 at the third and 1 at the fourth application. Of the exotropic patients, 15 received 2.5 u BTA at the first application, 6 at the second, 5 at third and 1 at the fourth application. Two patients who received 2.5 u BTA at the fourth repeat application in both groups were excluded from the study. The mean pre-treatment and post-treatment deviations, mean improvements, percentage reduction of initial deviation and standard errors are given in Tables III and IV for esotropic and exotropic patients respectively. The difference in the percentage reduction of initial deviation between three groups was analysed by the Kruskal–Wallis variance analysis method separately for both esotropic and exotropic patients. It was found to be statistically insignificant for both patient groups. This shows that regardless of the number of repeat doses applied, the percentage reduction of initial deviation with each repeat BTA application was similar.

Next the effect of the dose increment of BTA on the improvement in pre-treatment deviation was investigated. The patients who were treated with 2.5, 5, 10, 15 and 20 u BTA were evaluated in five groups. The mean pre-treatment and post-treatment deviations, mean improvement, percentage improvement as a function of pre-treatment deviation and their standard errors are shown in Tables V and VI for esotropic and exotropic patients respectively. The differences in percentage improvement among the five dose groups were analysed by the Kruskal–Wallis variance analysis method. For esotropic patients the difference was statistically significant ($p<0.05$). Further, we paired all five groups and investigated the significance between paired groups with the Mann–Whitney U-test. The relation between increasing effect of BTA and increasing dose was statistically significant only between groups 1 and 3 and groups 1 and 5 ($U = 100$, $p<0.05$; $U = 73$, $p<0.05$, respectively). This showed that the response to BTA treatment was increased by increasing the dose from 2.5 u to 10 u and from 2.5 u to 20 u. The dose-dependent effect of BTA could not be shown for small dose increments. The average percentage change in initial deviation for esotropic patients was found to be 46%. For exotropic patients the differences in percentage improvement among the five dose groups were also analysed by the Kruskal–Wallis variance analysis method. The dose–response relation was not statistically significant ($p>0.05$). For exotropic patients increasing the dose of BTA did not increase the response. The percentage correction of the initial deviation after botulinum application was found to be 29% for exotropic patients.

Lastly we evaluated the relation between the pre-treatment deviation and the percentage of patients having correction within 5 and 10 degrees of straight. The angle of deviation improved to 5 degrees of straight in 15 (33%) and to 10 degrees in 31 (68%) of 45 esotropic patients. When the patients were divided into four groups according to their initial angles of deviation, the percentage having a post-treatment deviation within 5 degrees of straight was

Table IV. The mean pre-treatment and post-treatment deviations, mean improvement and percentage reduction in initial deviations (± standard errors) for exotropic patients (min.–max.)

Injection no.	BTA dose (units)	Pre-treatment deviation (degrees)	Post-treatment deviation (degrees)	Mean improvement (degrees)	Correction (%)
1	2.5	18.9 ± 1.9 (7–36)	15.3 ± 2.2 (5–30)	4.0 ± 1.1 (0–5)	22.1 ± 5.3
2	2.5	18.5 ± 4.2 (6–30)	13.6 ± 3.9 (4–30)	4.8 ± 2.2 (0–12)	29.1 ± 6.7
3	2.5	12.8 ± 5.0 (2–30)	10.5 ± 6.5 (2–30)	3.5 ± 2.5 (0–11)	31.5 ± 9.9

Table V. The mean pre-treatment and post-treatment deviations, mean improvement and percentage reduction in initial deviations (± standard errors) with regard to changing BTA doses for esotropic patients. (min.–max.)

BTA dose (units)	Patients (*n*)	Pre-treatment deviation (degrees)	Post-treatment deviation (degrees)	Mean improvement (degrees)	Correction (%)
2.5	37	16.5 ± 1.2 (4–35)	11.2 ± 1.1 (0–26)	6.1 ± 1.1 (0–25)	30.2 ± 4.4
5	13	16.2 ± 2.2 (8–35)	9.7 ± 1.7 (2–25)	6.7 ± 1.3 (0–16)	40.3 ± 7.3
10	10	22.2 ± 3.9 (5–45)	8.5 ± 2.1 (3–23)	13.7 ± 4.2 (2–42)	53.7 ± 9.1
15	10	16.5 ± 1.5 (10–25)	8.1 ± 1.4 (0–15)	8.4 ± 1.9 (0–15)	48.9 ± 9.7
20	8	21.3 ± 3.6 (11–43)	10.3 ± 2.6 (0–23)	11.0 ± 1.2 (5–20)	56.3 ± 8.1

66% for group I, 36% for group II, 33% for group III, and 10% for group IV. The percentage having a post-treatment deviation within 10 degrees of straight was 100%, for group I, 90% for group II, 66% for group III and 30% for group IV (Table VII, Fig. 1).

The post-treatment deviation decreased below 5 degrees in 9 (18%) and below 10 degrees in 20 (40%) of 49 exotropic patients. The percentage having a post-treatment deviation below 5 degrees was 50% for group I, 10% for group II and 9% for group III. In none of the patients who had an initial deviation of more than 25 degrees were we able to achieve a post-treatment deviation below 10 degrees. The cosmetic success rates for these exotropic patients were 100% for group I, 20% for group II and 27% for group III (Table VIII, Fig. 2). Fig. 2 shows a tendency for less successful outcomes with increasing pre-treatment deviations.

We also evaluated the side effects of botulinum toxin injections. The distributions of patients who had post-injection ptosis, according to dose applied and type of strabismus, are summarised in Table IX. For our esotropic patients the incidence of ptosis after BTA treatment was 40%, 23%, 29%, 10% and 50% for patients receiving 2.5, 5, 10, 15 and 20 u BTA respectively. Ptosis disappeared completely in 4 weeks in all patients but one. In this patient, who had received 5 u BTA, ptosis disappeared in 6 weeks. For our exotropic patients the incidence of ptosis after BTA treatment was 14%, 14%, 11%, 27% and none for patients receiving 2.5, 5, 10, 15 and 20 u BTA respectively.

DISCUSSION

Botulinum toxin application is an alternative to strabismus surgery. This study was performed to evaluate the results of our experience and to answer some controversial questions such as the dose–effect relationship of botulinum toxin, the effect of repeat doses and the effect of initial deviation on post-treatment deviation.

We investigated whether the effect of repeat doses differed from that of the primary application. For both esotropic and exotropic patients we have found that repeat doses corrected the deviation to the same extent. It showed that there was no cumulative effect of the toxin but that the effect of each BTA application was independent of the previous one. While investigating the dose–effect relation of BTA we evaluated each BTA repeat injection applied as a separate patient. Some authors believe that the response to repeat BTA applications is no better for repeat injections while others report that secondary injections have a greater effect than primary injections.[2,3] They defined success as a post-treatment deviation within 10 pd of straight. The success rate increases with smaller angles of initial deviation so we have chosen the percentage reduction of initial deviation as a criterion for comparing the results of repeat doses. This allowed us to count each botulinum toxin application as one patient.

Table VI. The mean pre-treatment and post-treatment deviations, mean improvement and percentage reduction in initial deviations (± standard errors) with regard to changing BTA doses for exotropic patients (min.–max.)

BTA dose (units)	Patients (*n*)	Pre-treatment deviation (degrees)	Post-treatment deviation (degrees)	Mean improvement (degrees)	Correction (%)
2.5	27	17.1 ± 1.7 (3–36)	13.4 ± 1.7 (2–30)	4.0 ± 0.8 (0–15)	25.6 ± 3.9
5	28	12.5 ± 0.9 (2–25)	9.5 ± 0.7 (0–20)	3.5 ± 0.7 (0–18)	26.4 ± 4.5
10	17	17.4 ± 1.6 (6–30)	10.3 ± 1.3 (2–20)	7.0 ± 1.6 (0–20)	38.6 ± 7.0
15	11	21.6 ± 3.7 (7–45)	15.8 ± 2.9 (7–35)	6.7 ± 1.2 (0–16)	27.9 ± 6.3
20	4	19.2 ± 3.6 (10–25)	13.5 ± 3.3 (6–20)	5.8–2.2 (0–11)	28.2 ± 13.6

Table VII. The distribution of esotropic patients having post-treatment deviation within 5 and 10 degrees of straight according to their initial deviations

Initial deviation (degrees)	Total esotropic patients (*n*)	Post-treatment deviation <5 degrees (*n*)	Post-treatment deviation 6–10 degrees (*n*)
5–10	6	4	2
11–15	11	4	6
16–25	18	6	7
>25	10	1	2

We then investigated whether the effect of botulinum treatment was dose dependent. For esotropic patients we found the effect increased with the increase in dose of the toxin. It was more prominent between doses of 2.5 and 10 u, and 2.5 and 20 u. The average correction with a 2.5 u BTA application was 6.1 degrees, while the correction after 20 u was 11.0 degrees. The effect obtained almost doubles with this increase in dose. We were unable to show a difference in the effect of BTA with small increments in dose. This may stem from the uneven distribution of patients in each group. It is again hard to estimate the effect of botulinum toxin in a specific dose given, because although there is a trend towards larger effects for higher doses, individual results may show a variation between 0 and 100% correction. The increase in effect with increase in dose was previously mentioned by Scott but the doses involved were rather small.[4] We feel it is safe to use 20 u BTA in esotropic adults to achieve a larger effect. For exotropic patients we were unable to show a dose–response relationship. The variation was even higher for the exotropic patients. The average correction obtained with a 2.5 u BTA application was 4.0 ± 4.4 degrees, which increased to only 5.8 ± 4.6 degrees with an eightfold increase in dose. As the standard deviations were high, the predictability of the effects of BTA injections in exotropic patients was found to be low. This may result from the larger percentage of patients having consecutive and secondary deviations compared with the esotropic patients. It may also be related to the fact that the exotropic patients are less responsive to BTA application than the esotropic patients, so that increases in BTA doses would show a less significant increase in response.

The incidence of ptosis for exotropic patients was 14% and that for esotropic patients was 29%. The incidence of ptosis is higher for esotropic patients compared with exotropic patients. It has also been noted previously by several authors that ptosis was more common when the medial rectus muscle was treated with BTA.[5] In Scott's data ptosis was found in 16% of adults and 25% of children. As the numbers of patients in our groups receiving 15 and 20 u BTA are small, evaluating side effects according to the dose applied is not realistic. Overall for patients receiving 15 and 10 u BTA the incidence of ptosis was 20% for esotropic patients and 27% for exotropic patients. This also shows that higher doses of 15 and 20 u can be used without the risk of a higher incidence of side effects.

Our 45 esotropic patients received an average 1.7 injections (total of 80 injections). We achieved a post-treatment deviation within 5 degrees of straight in 33% and within 10 degrees in 68% of patients. The deviations were corrected by 45% of the initial deviation. We found that smaller deviations were more likely to achieve a result of less than 5 degrees post-treatment deviation than were moderate and large deviations for both esotropic and exotropic patients. This has been suggested previously by other authors.[6,7]

Magoon[8] reported that 35% of adults with horizontal strabismus were corrected to within 10 prism dioptres (pd) of straight. The results of Biglan and associates[7] are similar to ours as they found a 38% correction rate after an average of 1.3 injections in a mixed group of patients. Of their 32 esotropic patients with an average 22.8 pd initial deviation, 34% of them were controlled with the drug. They found that the results were more satisfactory for small deviations (e.g. <20 pd). Elston and colleagues[9] regarded the final deviation as acceptable if it was no more than 50% of pretreatment angle and the patient was satisfied with their appearance. In their study of 85 patients with 8 weeks follow-up, they had an average 60% reduction in initial deviation. But when the eighth week was taken into consideration the reduction rate appears to be 46%, which is very similar to our results in esotropic patients. Scott, who has the largest botulinum treatment series,

Table VIII. The distribution of exotropic patients having post-treatment deviation within 5 and 10 degrees of straight according to their initial deviations

Initial deviation (degrees)	Total exotropic patients (*n*)	Post-treatment deviation <5 degrees (*n*)	Post-treatment deviation 6–10 degrees (*n*)
5–10	10	5	5
11–15	10	1	1
16–25	22	2	4
>25	7	—	—

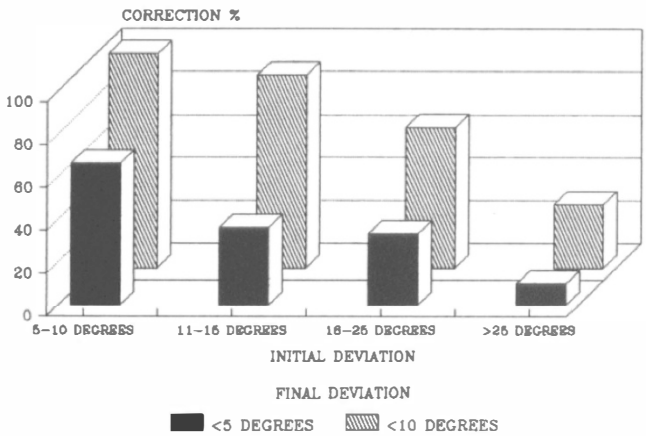

Fig. 1. *The percentage correction of deviation within 5 or 10 degrees of orthophoria with regard to initial deviation in esotropic patients.*

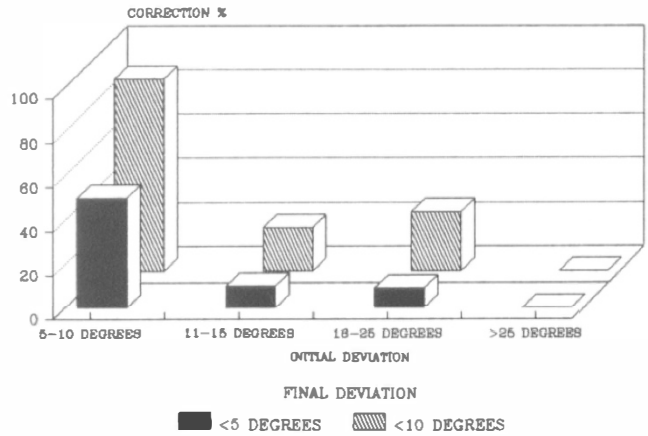

Fig. 2. *The percentage correction of deviation within 5 or 10 degrees of orthophoria with regard to initial deviation in exotropic patients.*

summarised his results in one of his studies.[6] He found that 57% of his 384 esotropic patients with an average initial deviation of 30 pd had a final deviation within 5 degrees of straight. They had an average 63% change in their initial deviation. When we evaluate our results with regard to initial deviation, those for esotropic patients are comparable to those of Scott. The deviations of esotropic patients with an initial deviation between 5 and 10 degrees were corrected to within 5 degrees of straight in 66%; Scott's figure was 72%. When the initial deviation increased to 16-25 degrees, the percentage correction to 5 degrees of straight decreased to 33%. In Scott's series, for esotropic patients with initial deviations greater than 40 pd the percentage having a final deviation within 10 pd of straight decreased to 35%.

In our 49 exotropic patients an average of 1.8 injections were given per patient (total of 91 botulinum injections). We achieved a post-treatment deviation within 5 degrees of straight in 18% and 10 degrees in 40% of patients. The deviations were corrected by 29% of the initial deviation. The mean magnitude of the initial deviation was 15.9 ± 0.8 degrees. The results in exotropic patients were less satisfactory than in esotropic patients. This finding has also been noted by several other authors.[2,7,10,11] In a study by Scott *et al.*[3] it was also shown that better results were obtained when treating esotropia than exotropia regardless of whether previous surgery has been performed. The higher success rate for medial rectus muscle injection might be related to the greater concentration of a global layer of singly innervated fibres in medial rectus muscle which are singularly and profoundly affected by botulinum.[12] Biglan and associates[7] achieved a 13% cure rate in their exotropic patients who had an average of 26.9 pd initial deviation. The mean reduction in magnitude of the deviation with drug was only 5 pd. They recommend traditional surgery for exotropic patients. Our data showed a similar cure rate in our exotropic patients but the mean reduction in the magnitude of deviation was 5.41 degrees. Carruthers and associates,[13] had a 25% cure rate in their exotropic patients, who had an average initial deviation of 33.7 pd. They recommended surgical treatment for exotropic patients without fusion. Scott[6] found that 67% of his patients with an initial deviation between 10 and 24 pd had a final deviation within 10 pd. Our patients with an initial deviation between 5 and 10 degees had a similar cure rate of 50%. When the initial deviation increased to 16–25 degrees the cure rate decreased to 9%. The equivalent figure in Scott's series for patients with an initial deviation greater than 40 pd was 33%. He had the best results for exotropic patients in the literature. This difference may stem either from the small number in our group of patients with a large initial deviation or from the greater variation in results of botulinum treatment with regard to esotropic patients.

We conclude that botulinum treatment is a good alternative to traditional surgery in concomitant horizontal deviations. The results of BTA treatment are more predictable for esotropic patients than for exotropic patients. The effect is dose dependent in esotropic patients. A larger patient group may help to demonstrate the same relationship in exotropic patients.

Table IX. The incidences of ptosis in esotropic and exotropic patients with respect to increasing BTA doses applied

BTA dose (units)	Esotropia		Exotropia	
	Ptosis (*n*)	Total (*n*)	Ptosis (*n*)	Total (*n*)
2.5	15	37	4	27
5	3	13	4	28
10	0	10	2	17
15	1	10	3	11
20	4	8	0	4

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Key words: Botulinum toxin A, Esotropia, Exotropia, Strabismus.

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