Early retreatment of infantile esotropia: comparison of reoperation and botulinum toxin

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Abstract

***Aim*—To compare the efficacy of reoperation and botulinum toxin injection in treating infantile esotropes early after unsatisfactory surgical alignment.**

***Methods*—55 strabismic children who had been unsuccessfully operated for infantile esotropia were randomised to reoperation (28 patients) or botulinum toxin injection (27 patients). The motor outcomes (percentage of successful motor outcome and percentage change in deviation) were compared at 6 months, 1 year, and 3 years after retreatment, and the sensory outcomes (percentage with fusion ability and stereo perception) at the 3 year follow up visit.**

***Results*—The motor and sensory outcomes and the stability of motor results were similar in patients reoperated and treated with botulinum injection. At the 3 year visit 67.8% and 59.2% of children were, respectively, within 8 prism dioptres of orthotropia (p=0.72). The frequency of fusion ability was, respectively, 60.7% and 51.8% (p=0.71), and the frequency of stereo perception (⩽400 seconds of arc, Randot circles), 57.1% and 48.1% (p=0.70). The botulinum injection was more likely to be effective when carried out in the 6 months following initial surgery.**

***Conclusions*—Botulinum injection is a rapid and less invasive alternative to reoperation in children who have been unsuccessfully treated with surgery to correct infantile esotropia.**

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In a recent study, botulinum toxin injection was found to be as effective as reoperation in the retreatment of children previously operated to correct an acquired esotropia, particularly in early failures or patients retreated soon after the primary procedure.[1] After surgery for infantile esotropia it is also necessary to retreat children in many cases. Often motor success is defined as a deviation equal to or less than 8 or 10 prism dioptres. The motor success rates of 50–65% with the traditional 5 mm maximum for recession of the medial recti[2–5] improved to 84% with recessions measured from the corneoscleral limbus or augmented recessions.[6–9] It follows that about 20% of patients may need a second procedure. Undercorrections are usually predominant among failures,[2–5 7–9] but other authors have also found overcorrections in a considerable number of results.[6] Although the proportion of infantile esotropes who require a secondary procedure is near to that found for acquired esotropes, it is questioned whether the sensory results obtained in the former category may be as good as in the latter.[10–13]

In this study we compare the efficacy of the two extant therapeutic options—reoperation and botulinum toxin—after an unsatisfactory result of surgery for infantile esotropia, a clinical setting with presumably less fusional and stereo perception potential than acquired esotropia.

Methods

We included in the study children with infantile esotropia who required a second procedure for alignment in whom the initial surgery was performed between 1990 and 1994. Participants should have been operated for the first time before 24 months of age and retreated in the subsequent 12 months. Our purpose was to limit the groups to cases that were never orthophoric after the first treatment. We included patients with history of esotropia present in the first 6 months of life. Patients with a distance to near difference of at least 10 prism dioptres or in whom the correction of hypermetropia with spectacles improved or corrected the esotropia were excluded. Children with vertical deviations greater than 4 prism dioptres, and those with medical or neurological disease were also discarded. Selected patients were randomised to reoperation (28 patients) or botulinum toxin injection (27 patients) to correct at least 12 prism dioptres of deviation. The characteristics of the two groups of patients are summarised in Table 1.

The methodology was similar to that used in our earlier investigation on acquired esotropes. We carried out refractions 30–45 minutes after instillation of 1% cyclopentolate hydrochloride. Hypermetropia greater than +2.00 dioptres was corrected with glasses. The angles of deviation were measured by the simultaneous prism and cover test and the prism and alternate cover test at 6 and 0.33 metres in the different gaze positions, or with the Krimsky method when the cover tests were not practicable. The Worth 4 dot, the Bagolini lenses, the Randot circles, and the TNO test were used to evaluate the sensory state after the secondary treatment (at the 3 year follow up visit). Children with presumed amblyopia underwent therapy before the secondary procedure. All the participants were able to maintain fixation through a blink with the less preferred eye before retreatment.

The patients in the two groups had been treated with only one previous documented

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Table 1 Characteristics of the treatment groups

	Reoperation group (28 patients) mean (SD)	*Botulinum toxin group (27 patients) mean (SD)*	*p* Value*
Age at initial surgery (months)	15.33 (3.31)	14.25 (3.12)	0.22
Amount of bimedial recession in primary procedure (mm)	5.75 (0.60)	5.50 (0.45)	0.07
Time between the two procedures (months)	6.25 (1.60)	5.50 (1.23)	0.06
Angle before retreatment (prism dioptres by simultaneous prism and cover test)			
Distance	25.40 (11.35)	20.27 (15.15)	0.16
Near	28.87 (12.41)	24.12 (16.02)	0.22
Spherical equivalent before retreatment (dioptres)	2.28 (1.70)	2.06 (1.34)	0.58
Visual acuity ratio before retreatment (amblyopic eye/sound eye)	0.81 (0.13)	0.83 (0.19)	0.65
Follow up after retreatment (years)	3.75 (0.12)	3.50 (0.21)	<0.0001

*Unpaired Student's *t* test.

operation. Initial surgery was a bimedial recession procedure. Reoperation was performed by the same surgeon with careful dissection of muscles and removal of fibrotic tissue. In undercorrected children we made bilateral lateral rectus resection, following previously published guidelines.[14] When restriction was detected medially by forced duction at the time of reoperation we did small amounts of bilateral medial rectus rerecession,[15] and the conjunctiva was always recessed. For overcorrections we carried out bilateral lateral rectus recession,[14] unless we found weakness in adduction, for which we preferred to advance the medial recti muscles.[16] In the botulinum toxin group, botulinum toxin type A (Botox, Allergan) was administered under topical anaesthesia alone (0.5% proxymetacaine (proparacaine) hydrochloride) or in combination with mild general anaesthesia (ketamine intramuscularly/intravenously or nitrous oxide inhalation). We used the maximal dosages suggested by Scott *et al.*[17] The toxin was injected into one or two (when total dose >5 U) recti muscles with electromyographic control. The secondary treatment procedures are listed in Table 2.

The follow up in all the cases under study was of at least 36 months. For statistical comparison we used the motor success rate and percentage net change in the deviation (preoperative deviation − postoperative deviation/preoperative deviation × 100%) at 6 months, 1 year, and 3 years after the second treatment, and the fusion and stereo perception at the 3 year follow up. Successful motor alignment was defined as a distance deviation of 8 prism dioptres or less by the simultaneous prism and cover test. Fusion was detected by the Worth 4 dot at near and the Bagolini lenses, and the presence of stereopsis with the Randot circles (at least 400 seconds of arc) and TNO test (at least 480 seconds of arc).

The information recorded included the following: age at presentation and diagnosis of strabismus, sex, refraction and best corrected visual acuity, age at first and second treatment (and time interval between the two), angle of deviation before retreatment, angle of deviation 2 months after retreatment, at 6 months, at 1 year, and at 3 years, fusion ability and stereo perception at 3 years after retreatment, surgical procedures performed, and dose of botulinum toxin when used.

The unpaired Student's *t* test or Mann–Whitney U test were used to evaluate differences between means of continuous data. χ^2 analysis or Fisher's exact test were used to compare percentages.

Table 2 Secondary treatment procedures

Reoperation group (28 patients)		*Botulinum toxin group (27 patients)*	
Resection lateral recti	14 esotropes	3–12.5 U in medial recti	25 esotropes
Re-recession medial recti	10 esotropes	3–5 U in lateral rectus	2 exotropes
Recession lateral recti	3 exotropes		
Advancement medial recti	1 exotrope		

Results

Fifty five patients were enrolled in the study. Twenty eight patients were reoperated (13 girls and 15 boys) and 27 were treated with botulinum toxin injection (12 girls and 15 boys). In the reoperation group, the second surgery was aimed at the correction of residual esotropia (undercorrection) in 24 of the 28 patients, while in four of them it was undertaken to achieve the correction of consecutive exotropia (overcorrection). In the botulinum toxin group, 25 of the 27 patients were esotropic and only two of them were injected to correct a consecutive exotropia.

In the reoperation group 21 out of 28 patients (75%) were within 8 prism dioptres of orthotropia 6 months and 1 year after reoperation, and 19 out of 28 patients (67.85%) were within these limits 3 years after reoperation. In the botulinum group, 18 of 27 patients (66.66%) were in the motor successful range 6 months after injection, whereas 1 year and 3 years after injection 17 patients (62.96%) and 16 patients (59.25%), respectively, were in the motor successful range. The percentage of patients with successful motor outcome was similar in the reoperation group and in the botulinum toxin group (χ^2test) at 6 months (75% *v* 66.66%; p=0.72), at 1 year (75% *v* 62.96%; p=0.50), and at 3 years (67.85% *v* 59.25%; p=0.72). The motor success percentage declined over the follow up in the two treatment groups but the values did not change significantly in this intervening period. Figure 1 represents the motor stability over the follow up period.

The average net change in deviation observed was similar in the two groups (Mann–Whitney U test). The secondary surgery produced 82.02% of average change in deviation when evaluated at 6 months, and the botulinum injection produced 78.71% change (p>0.05). At 1 year these values were, respectively, 80.25% and 71.27% (p>0.05), and at 3 years 76.32% and 68.46% (p>0.05).

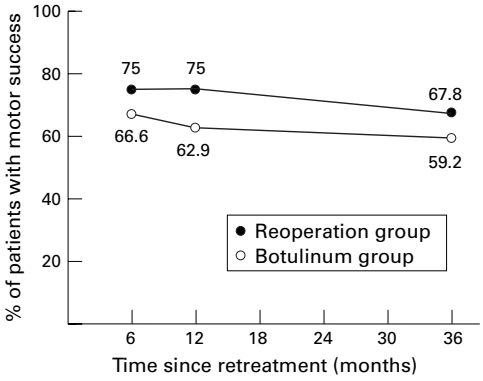

Figure 1 Percentages of patients with motor success in the two treatment groups at different moments of the follow up after retreatment (months). Motor success is defined as deviation of 0–8 prism dioptres by the simultaneous prism and cover at 6 metres. The percentages observed are similar in the two groups at 6 months (p=0.72), 1 year (p=0.50), and 3 years (p=0.72). The stability of the motor success rates over the follow up is noticeable.

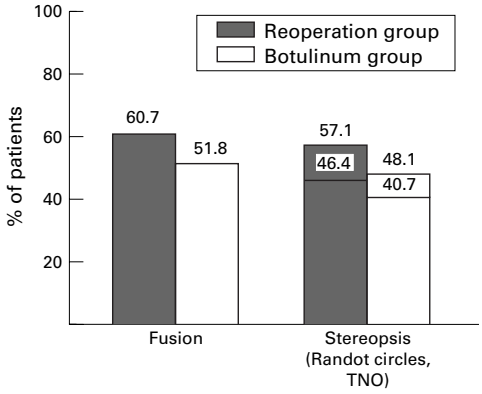

Figure 2 Percentages of patients with fusion and stereo perception in the two treatment groups. Fusion was acceptable when detected by both the Worth 4 dot at near and the Bagolini lenses. The upper values in the stereopsis bars correspond to the percentages obtained with the Randot circles (at least 400 seconds of arc) and the lower values to those with the TNO test (at least 480 seconds of arc). The difference is not significant in the fusion (p=0.71) and in the stereo perception percentages as measured by the Randot circles (p=0.70) and TNO (p=0.90).

We evaluated the sensory state at the 3 year visit (see Fig 2). The same proportion of children with fusion ability and stereo perception was found in the two treatment groups (χ^2 test). Fusion on the Worth test at near and the Bagolini lenses was present in 17 of 28 reoperated children, and in 14 of 27 children injected with the toxin (60.71% *v* 51.85%; p=0.71). Stereo perception of at least 400 seconds of arc on the Randot circles was detected in 16 patients in the reoperation group and in 13 patients in the botulinum group (57.14% *v* 48.14%; p=0.7). When we used the TNO test, 13 and 11 patients, respectively, had at least 480 seconds of arc of stereopsis (46.42% *v* 40.74%; p=0.9).

It is suspected that botulinum toxin is more effective when injected soon after preceding conventional surgery. Yet we could not demonstrate that this treatment was superior when applied in the first 3 or 6 months after initial surgery relative to the cases injected later (Fisher's exact test). Five of seven patients treated in the first 3 months, and 12 of 20 patients injected after this borderline, were successfully aligned at 1 year (71.42% *v* 60%; p=0.45, one tail). Ten of 13 patients injected in the first 6 months and seven of 14 treated later were in the motor success range (76.92% *v* 50%; p=0.14, one tail). Ptosis occurred transiently in 10 of the 27 patients injected with botulinum toxin (37.03%) and vertical deviation was also temporary in five of them (18.51%).

Discussion

The botulinum toxin injection is an operative therapy in the early management of infantile esotropes who have not been successfully corrected with conventional surgery, and this therapy may be considered as effective as reoperation. The motor and sensory results obtained in this study are similar with the two treatments (percentage net change in deviation, realignment success rate, proportion of patients who achieved fusion, and stereo perception). This conclusion is applicable to patients who were never orthophoric after surgery in whom retreatment is carried out in the relatively early postoperative period of 1 year.

The sample sizes in the present study may be considered a design limitation, since treatment difference could be missed when they are not large enough. However, the power of the statistical tests we have used varies between 81% and 90% at the 0.05 significance level. Therefore, the chance of finding a significant difference if real differences exist between the two groups is high.

The exclusion criteria used in this investigation are directed to eliminate patients who can dubiously be classified as infantile or early onset esotropes. This minimises the probability of having acquired esotropes in the treatment groups but it is not absolutely ruled out. The proportion of undercorrected and overcorrected children that resulted from our selection are comparable with previously published outcomes of surgery for infantile esotropia.[2–5 7–9] Most of the selected cases were residual esotropes, but this is the prevailing unsatisfactory result in these articles. Before the introduction of augmented recession of medial recti some authors reported a high rate of undercorrections (40–50%), while that of consecutive exotropia did not exceed 8%.[2–5] With larger recessions overcorrections were also considered to be infrequent or negligible,[7–9] but a considerable proportion of them has also been found among failures.[6]

After one strabismus operation for infantile esotropia 50–84% of patients are aligned within 8 or 10 prism dioptres.[2–9 18] According to Helveston,[19] after a reoperation 33% of patients may need further surgery for realignment, which may be comparable with the results in this study. King *et al* [15] obtained 40.62% success rate after rerecession and 57.5% after bilateral lateral rectus resection. These are lower success rates compared with our results, but they include different categories of residual esotropes with larger average deviation.

Studies of botulinum toxin including non-operated infants and children (with or without

some operated cases) report satisfactory success rates even after long term follow up.[17 20 21] Biglan *et al* [22] injected 56 patients after surgery, including both esotropes and exotropes, and obtained for overcorrections (eight patients) 84% of corrected deviation with 87.5% of patients controlled, which is better than our global results. We injected two overcorrected patients and only one was within the successful motor range at the end of the follow up. For residual deviations (48 patients) they reported 46% of corrected deviation and 41.6% of patients controlled, an inferior outcome compared with our botulinum group in which 25 of the 27 patients were residual esotropes. Magoon[20] obtained 85% correction for esotropes in the amount of deviation and for exotropes 79–83%, with a global successful motor outcome rate of 85%. These results are better than those reported in this study, but of the 85 patients only two were injected after incisional surgery. Our results are closer to the study by Scott *et al*[17] on childhood strabismus, who obtained 66% of final success in undercorrected esotropia (63% change in deviation) and 57% in exotropes after overcorrection of esotropia (48% change in deviation). In the global category of infantile esotropes with previous surgery, 65% had successful motor alignment (61% change in deviation).

Thus, there is no agreement about whether botulinum injection is more effective in treating undercorrected or overcorrected esotropia.[17 22] A way of reasoning argues that the greater concentration of singly innervated fibres in the medial rectus muscle[23] makes it easier to paralyse than the lateral rectus, although one has to penetrate deeper and through scar tissue to inject a recessed medial rectus. In addition, when the lateral rectus is injected for consecutive exotropia, the recessed medial rectus has less potential to shorten or strengthen in response to paralysis of the antagonist (but with the advantage that the lateral rectus is untouched). Following these arguments, undercorrection of esotropia would be managed better than overcorrection with botulinum toxin, but this point remains to be clarified. The present study was not designed to answer this point.

A previous investigation[17] considered that the efficacy of botulinum toxin is the same in operated than in non-operated children. This is attributed to the elasticity of the muscles in children. In operated cases the angle sizes are usually smaller than in those not previously operated, and this might also contribute to the improved results obtained with botulinum toxin in the former group, in spite of potential scarring from preceding surgery.

The outcomes after botulinum injection are also satisfactory in previously operated acquired esotropes.[1] These are slightly favourable when compared with infantile esotropes; the fusional potential in the acquired group might account for this, but the difference could be negligible.

The frequency of side effects observed after botulinum toxin injection—namely, transient ptosis and vertical deviation, approaches the highest values of frequency reported in patients not operated before.[17 20 22 24–26] This is related to the difficulty of needle access in children who have undergone previous surgery.

The influence of postoperative delay after initial surgery on the efficacy of botulinum injection cannot be precisely defined from our data. It seems that botulinum retreatment within 6 months of surgery would be desirable, since a nearly statistically significant difference exists between the motor outcomes of children injected before and after this time.

An interesting point is that the successful alignment rates obtained with botulinum injection decline only slightly with time, but this trend is also observed in the group of patients who underwent a second surgery. Thus, the reported permanence of alignment after long term follow up of children treated with botulinum toxin,[17 20 21] with some of the patients injected after surgery, may be extended to patients previously operated for infantile esotropia.

The use of botulinum toxin avoids the production of significant scar tissue and, if unsuccessful, leaves the door open for repeating surgery. This injection would increase or reduce the effect produced by surgery. An objection is that alignment is delayed by the use of the toxin because the induced paralytic deviation may persist for more than 3 months. Hypothetically, this delay could be harmful in some cases, but the precise moment before which correction of the misalignment is advisable (to avoid loss of binocularity) remains unknown. In addition, if we must perform surgery again we probably should have to wait until the effect of the toxin subsided (this effect can last over 6 months) so that the surgical plan was based on a deviation not influenced by the remaining paralysing effect of the drug.

In summary, this study indicates that the use of botulinum toxin after postoperative failure of surgery for infantile esotropia is an alternative to repeated conventional surgical therapy. The two are equally effective after 3 years of follow up, but the botulinum technique is safe, more rapid, and less invasive.

None of the authors has any interest in the products or devices mentioned here.

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