RAPID COMMUNICATION

Surgery with intraoperative botulinum toxin-A injection for the treatment of large-angle horizontal strabismus: a pilot study

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INTRODUCTION

Some patients with large-angle strabismus may refuse or may not meet the criteria for binocular surgical correction. A second option for these patients involves a monocular procedure, which can be performed under peribulbar anesthesia and offers certain advantages (1).

Improved surgical outcomes for conventional procedures may enhance the effectiveness of monocular surgery. In theory, this enhancement could be achieved by the coadjuvant use of intraoperative botulinum toxin A (BT) (2). To date, few reports have described the intraoperative injection of BT (3-5).

Owens et al. (3) performed supramaximal monocular recession-resection surgeries and successfully used intraoperative BT in three large-angle exotropia patients. Khan (4) successfully performed two-muscle horizontal rectus surgery with simultaneous BT injection in patients with severe large-angle esotropia. Additionally, seven patients underwent bilateral medial rectus recession and bilateral BT injection, and one patient underwent a unilateral recess/resection surgery with medial rectus BT injection. These results indicated that bilateral medial rectus recession with simultaneous BT injection is a safe and effective surgical procedure for patients with severe large-angle esotropia, although more extensive studies are required to confirm these findings. Oskan et al. (5) reported the results of 10 patients with large-angle horizontal deviations (eso- or exotropia) who received BT injections into one recessed muscle and concluded that such treatment may provide greater surgical success compared to conventional horizontal rectus muscle surgeries.

The results of these uncontrolled studies have reinforced the hypothesis that long-term realignment of the eyes can be achieved with surgery plus BT administration. However, the effectiveness of the addition of intraoperative BT compared to surgery alone is unclear.

In this pilot study, we used a prospective, controlled, and randomized double-blind methodology to examine the effectiveness of BT injection in combination with surgical treatment compared to surgical treatment alone for the correction of large-angle horizontal deviations under local anesthesia.

PATIENTS AND METHODS

The study population was composed of adult patients 18 years of age or older who had concomitant horizontal deviations (eso- or exotropia) of 50 pd or more. Patients who had undergone previous surgical treatment or who had neurological or systemic disease, oblique muscle dysfunction, dissociated vertical deviations or other clinically significant vertical deviations, or parietic or restrictive strabismus were excluded from the study.

The preliminary information that was recorded for each patient included the age at which strabismus was detected and diagnosed, the best-corrected visual acuity (BCVA), the frequency of severe amblyopia (BCVA less than 0.5 without other anatomical eye abnormalities), the angle of deviation before treatment, the surgical plan (mm of recess/resection), and the surgery ratio (angle of pretreatment deviation divided by the sum of mm of recess plus mm of resection). Snellen visual acuity was converted to LogMAR acuity prior to statistical analysis (6) and then converted back to the Snellen equivalent.

The study was designed to include 11 patients in each group. This sample size was chosen based on previously published reports of monocular recess/resection surgeries for the correction of horizontal strabismus (1).

The patients were randomized to the surgery plus hyaline solution (SG) treatment group or to the surgery plus botulinum toxin-A (SG+BT) treatment group. The investigators were blinded to the patients’ treatment groups.

All of the patients underwent a complete ophthalmological and motor evaluation prior to surgery. The angles of deviation were measured with the best optical correction in place for the distance and the near and cardinal gaze positions. The measurements were made using the simultaneous- and alternate-cover tests, and the Krimsky test was employed when the cover tests were not applicable.

The surgeries were performed between November 2006 and June 2007 by the main investigator. The patients underwent recess/resection surgeries on the non-fixating eye using conventional techniques (7) under local anesthesia. All patients received 5 mg of oral diazepam 30 minutes before anesthesia. An intravenous line, oxygen nasal cannula, cardiac monitoring and continuous pulse oximetry were employed during the surgeries. The local anesthetic...
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Table 1 - Summary of descriptive characteristics of the patients.

|                        | SG+BT | SG   | p-value |
|------------------------|-------|------|---------|
| Age at surgery (years)* |       | 34.3 ± 6.4 | 28.8 ± 9.8 | 0.08 |
| Angle of preoperative deviation in pd* | 65.8 ± 14.9 | 60.0 ± 16.9 | 0.27 |
| Surgery ratio (pd of preop dev/mm of surgery)* | 4.26 ± 0.85 | 3.86 ± 0.92 | 0.16 |
| Fixing eye BCVA (LogMAR)* | BC | 0.08 ± 0.29 | 0.11 ± 0.30 | 0.53 |
| Non-fixing eye BCVA (LogMAR)* | 0.87 ± 0.76 | 1.03 ± 1.14 | 0.93 |
| Non-fixing eye BCVA (0.5 or worse; LogMAR)* | 1.15 ± 0.67 | 1.57 ± 1.10 | 0.42 |
| Fixing eye BCVA (decimal)** | 0.67 | 0.5 | 0.66 |
| Non-fixing eye BCVA (decimal)** | 0.9 | 0.8 | 0.1 |
| Non-fixing eye BCVA (0.5 or worse; decimal)** | 0.07 | 0.03 | |

*mean ± SD.
**mean values.
BCVA = best corrected visual acuity.
Pd = prism diopter.
BT = botulinum toxin.
SG = surgery.

Table 2 - Numerical data for the variables.

|                  | Initial deviation | Recession | Final deviation |
|------------------|-------------------|-----------|----------------|
|                  | (dp)              | (mm)      | (dp)           |
| SG+BT            |                   |           |                |
| 1                | 1.0/0.1           | XT 90     | 9 - 8          | XT 15          |
| 2                | 1.0/0.3           | XT 60     | 8 - 6          | 0              |
| 3                | 1.0/CF            | ET 85     | 7 - 9          | ET 15          |
| 4                | 1.0/1.0           | XT 60     | 9 - 8          | XT 25          |
| 5                | 0.1/1.0           | ET 80     | 7 - 9          | ET 15          |
| 6                | 1.0/0.8           | XT 50     | 8 - 8          | ET 10          |
| 7                | 1.0/0.3           | ET 50     | 6 - 8          | 0              |
| 8                | 0.5/1.0           | XT 50     | 8 - 7          | ET 12          |
| 9                | 0.15/1.0          | ET 70     | 7 - 8          | *              |
| 10               | 1.0/CF            | XT 80     | 9 - 7          | ET 40          |
| 11               | 1.0/1.0           | ET 65     | 7 - 9          | *              |
| 12               | CF/1.0            | ET 50     | 6 - 8          | ET 8           |
| SG               |                   |           |                |
| 1                | 1.0/1.0           | XT 50     | 8 - 7          | XT 5           |
| 2                | 1.0/CF            | XT 50     | 9 - 6          | XT 15          |
| 3                | 0.1/0.1           | XT 65     | 9 - 7          | XT 15          |
| 4                | 1.0/1.0           | XT 50     | 8 - 8          | XT 6           |
| 5                | 1.0/0.1           | XT 50     | 9 - 7          | XT 15          |
| 6                | 1.0/0.2           | ET 50     | 6 - 8          | ET 15          |
| 7                | 0.9/1.0           | ET 90     | 7 - 9          | ET 40          |
| 8                | 1.0/CF            | XT 50     | 8 - 7          | XT 35          |
| 9                | 0.7/0.5           | XT 50     | 9 - 6          | XT 20          |
| 10               | 1.0/CF            | ET 60     | 7 - 8          | ET 15          |
| 11               | 1.0/0.6           | ET 95     | 7 - 10         | ET 25          |

SG = surgery only.
SG+BT = surgery with botulinum toxin injection.
BCVA = Best-corrected Snellen visual acuity.
CF = count fingers.
XT = exotropia.
ET = esotropia.
Mm = millimeters.
Pd = prism diopter.
*Missing values.

RESULTS

Twenty-three patients underwent operations; of these, 12 patients (6 females and 6 males) were assigned to the SG+BT group, and 11 patients (6 female and 5 males) were assigned to the SG group. Table 1 summarizes the descriptive variables for the two groups.

Table 2 presents the values of visual acuity, the pretreatment deviation angles, the amount of recess-resection, and the residual deviation for every patient included in the study.

This study was approved by the Ethics Committee of the Faculty of Medical Sciences at the State University of Campinas and complied with the principles of the Declaration of Helsinki (8). Informed consent was obtained from each patient who participated in the study.

The outcome data were collected by the main investigator, who was unaware of the treatment assignment, except in cases where ptosis had occurred. Angles of deviation were measured one day, two weeks, one month, three months, and 6-12 months (last visit) after the surgical intervention, and any adverse effects were recorded.

The percent net changes in the deviations [(preoperative deviation - postoperative deviation) / preoperative deviation × 100] were compared between groups at one day, two weeks, one month, three months, and 6-12 months after treatment. The percent net changes were also analyzed over time by comparing the values for the first and last postoperative visits between groups. There were not separate strata for patients with esotropia and those with exotropia.

The Mann-Whitney test was used to evaluate the differences between the mean values of continuous data, and Fisher’s exact test was used to compare percentages. An analysis of variance (ANOVA) with rank transformation was used to analyze the evolution of percent net change. All data analyses and statistical comparisons were performed using the SAS (Statistical Analysis System) software for Windows (version 9.1.3) and Microcal Origin (version 5.0). The level of significance was set at 5%, i.e., for p-values ≤0.05.

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consisted of 0.5% bupivacaine without epinephrine and 2% lidocaine with epinephrine. The extent of surgical recess/resection was determined based on typical read-out values (Table 1). Before reattaching the recessed muscle to the sclera, the surgeon injected the posterior muscle belly with 0.1 ml of hyaline solution alone (SG) or 5 units of BT (Prosign®, Cristália, Campinas, Brazil) in 0.1 ml of hyaline solution (SG+BT). The surgeon was unaware of the contents of each syringe.

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Table 1 - Summary of descriptive characteristics of the patients.

|                        | SG+BT | SG   | p-value |
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| Age at surgery (years)* |       | 34.3 ± 6.4 | 28.8 ± 9.8 | 0.08 |
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Six patients in the SG+BT group had esotropia, four of which had presumably infantile esotropia and two had partially accommodative esotropia. Of the six patients with esotropia in this group, four had basic esotropia and two had sensory esotropia. In the SG group, there were four patients with esotropia, and each of these patients had presumed infantile esotropia. Of the seven patients in this group with esotropia, four had basic esotropia and three had sensory esotropia.

The percent net changes in postoperative deviations during the follow-up periods are shown in Table 3. These values were only significantly different between the groups at the one-month postoperative visit (p=0.05), when patients in the SG+BT group exhibited a larger percent net change in their deviations than did the control patients. A comparison of the results between the first and last follow-up visits revealed a significant decrease in the percent net change in both groups (p=0.0001), but there was no difference between the two groups (p=0.59).

Ten of the 12 patients in the SG+BT group attended the final follow-up visit at 6-12 months post-surgery. Eight of these patients exhibited satisfactory results, and four of these demonstrated orthotropia within 8 pd. The remaining two patients had unsatisfactory results and underwent a secondary operation. All eleven patients in the SG group attended the final follow-up visit at 6-12 months post-surgery. Seven of these patients had satisfactory results, and two of these demonstrated orthotropia within 8 pd. The results were unsatisfactory (more than 15 pd) for the remaining four patients in this group (Table 1).

Transient ptosis was observed in 5 of the 12 patients in the SG+BT group, and temporary vertical deviation was observed in one patient. No patients suffered from adverse effects related to surgery or anesthesia in the SG group. Furthermore, no patients demonstrated fusion or diplopia at the last follow-up visit.

**DISCUSSION**

In this study, we compared the results of surgery alone versus surgery plus treatment with BT for the correction of strabismus. Although there was a significant increase in the percent net change in the deviations between 7 and 30 days post-BT injection, this effect did not persist longer than three months. In addition, both groups exhibited similar decreases in the percent net change of the first post-operative measurement compared to the measurement at the final visit.

As all of the participants in this study were adults and demonstrated no evidence of fusion, the misalignment corrections were performed mainly for psychosocial benefit. The overall rate of surgical success was considered satisfactory, as 72% of the patients exhibited final deviations less than or equal to 15 pd.

BT can have a transient effect on extraocular muscles (9). Additionally, as noted elsewhere (10), in the absence of sensory and motor binocularity, there is a strong tendency for the recurrence of deviations in BT-treated patients, and this was also observed in our study. However, it is likely that BT treatment may alter long-term ocular alignment in children with fusion potential (11,12).

Certain studies have suggested a long-term, adjunctive effect of BT administration on surgical outcome, even in patients without fusion (3-5). Owens et al. (3) observed stable orthotropia at 2.5 years, stable 8-pd esotropia at 4 years, and stable 18-pd esotropia at 7 months in his case series of 3 patients. Oskan et al. (5) described the results for 10 patients (three children and seven adults with no preoperative fusion) with large-angle esotropia and exotropia who were treated intraoperatively with BT during strabismus surgery. After an average follow-up period of 14 months, they discovered that 70% of the patients exhibited alignment within 10 pd of esotropia or exotropia. Khan (4) described the results of eight patients who underwent two-muscle horizontal rectus surgery with a simultaneous intraoperative injection of BT into the medial rectus. Six of these eight patients demonstrated residual esotropia of less than 10 pd. This procedure was therefore considered safe and effective, although a more extensive study was suggested to be necessary to confirm the findings. This author later expressed disappointment with the results of a one-muscle injection of BT in the setting of a maximal recession-resection procedure for very large comitant esotropia and exotropia (unpublished data) and attributed this result to poor vision in one eye (the original motive for the monocular procedure) (13). In these three sets of cases, it is not possible to predict how the outcomes may have varied if the patients had undergone surgeries without BT injections.

Two characteristics of the current study enhanced our confidence with the results: the randomization of patients into one of two treatment modalities and the similarity between the two patient groups. These two factors helped to minimize the effects of other variables on the outcomes. The groups were similar in regards to visual acuity, frequency of amblyopia, state of binocularity, pretreatment angle of misalignment, and extent of surgery. Therefore, we believe that BT injection would have been the main factor to account for any differences between group outcomes, if any differences had been found.

It is possible that the incidence of transient ptosis could be reduced by injecting the recess muscle several days prior to surgery. Intact tissues not ruptured by surgery would hold the toxin in the muscle belly, thereby preventing it from spreading to adjacent tissues. The preoperative injection could be performed while monitoring with electromyography; also, some practitioners may waive the use of this device (14-16).

Our reported incidence of transient ptosis (42%) was higher than that in other studies. For example, Rowe and

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**Table 3 - Percent net changes in the postoperative deviations.**

| Post-operative interval | One day | 7-15 days | 30days | 90 days | ≥6 months |
|-------------------------|---------|-----------|--------|---------|-----------|
| SG+BT                   | 95.0 ± 16.2 (9) | 109.6 ± 24.1 (11) | 100.3 ± 17.5 (10) | 83.4 ± 17.9 (9) | 79.4 ± 15.7 (10) |
| SG                      | 101.9 ± 19.3 (7) | 92.3 ± 21.9 (9) | 83.0 ± 17.6 (10) | 71.4 ± 12.0 (6) | 69.0 ± 16.5 (11) |
| p-value                 | 0.63     | 0.15      | 0.05   | 0.19    | 0.10      |

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Noonan (17) reported an incidence of 8.4% for 511 patients who were treated with 3 U of BT (injected into the horizontal recti) to treat different types of strabismus. Additionally, Dawson and Sainani (18) reported an incidence of 4% for 503 patients who were treated for secondary strabismus. For studies that used intraoperative BT injections, Owens et al. (3) reported ptosis in two of three patients, Özkcan et al. (5) observed no ptosis in ten patients who were treated intraoperatively with 5 U of BT, and Khan (4) did not comment on ptosis in his study.

With regards to the dose-effect factor, a recent review of the literature concluded that it is not possible to determine the ideal BT dose-effect due to the different types and doses of botulinum toxin that were used in published trials (19). We chose to use 5 U per patient because this was the dose that had most commonly been used by other authors and because higher doses carry the risk of increased adverse effects (20).

None of the patients in this study hadduction limitation or lateral gaze diplopia, and none complained of a reduction in their visual field. These three adverse effects, in addition to exophthalmos, are typically expected when supramaximal plans are performed.

This study had several limitations. First, the physician who assessed the patient outcomes was unaware of the administered treatments during the data collection, except for the evaluation of patients with ptosis. Although this limitation was absent at the time of the final visit, the potential for ascertainment bias could not be refuted, despite efforts made to conduct an unbiased study.

As the treatment groups contained a mixture of esotropic and exotropic patients, it would be interesting to include a post-hoc analysis in each group (and in the eso- and exotrophia subgroups) to compare the efficacy of BT administration. However, the frequency of BT-induced ptosis prevented us from increasing the sample size to make such a comparison, although other studies on the usefulness of BT injection for strabismus treatment have found no association between the reduction in the angle of deviation and the type of deviation (20-22).

Based on the present findings, it appears that intraoperative BT injection does not enhance the effect of monocular horizontal deviation surgery. However, as this was a pilot study, the sample size was small, and this may have masked a real, albeit minor, therapeutic effect of intraoperative BT injection.

This study was presented at the XVIII Congress of Latin American Consul of Strabismus (CLADE) in November 2010. This study was performed in the Clinical Hospital of the State University of Campinas (UNICAMP) in Campinas, SP, Brazil.

Brand name of Botulinum Toxin A = ProsignR (Cristália, Campinas, Brazil). The authors do not have any commercial or proprietary interests in this product or company.

AUTHOR CONTRIBUTIONS

Minguini N contributed to the conception and the design of the project, acquisition of data, analysis and interpretation of the data, draft and writing of the manuscript, critical revision for important intellectual content, and also approved the final version of the manuscript to be published. Carvalho KM contributed to the conception and design of the project and assisted with critical revision of the manuscript for important intellectual content, and also approved the final version of the manuscript to be published. Bosso FL and Hirata F contributed to the conception and design of the data. Kara-Jose N contributed to the analysis and interpretation of the data and critically revised the article for important intellectual content.

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