# Pharmacologic Injection Treatment of Comitant Strabismus

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### Acknowledgements

Supported by National Institutes of Health, National Eye Institute grant R01-EY018633 to ABS & JMM, by the Pacific Vision Foundation (pacificvisionfoundation.org), by The Strabismus Research Foundation (srfsf.org), and by São Paulo Research Foundation (FAPESP) grant 2014/06807-6.

### Disclosures

ID: none

JMM: Orbit™ 1.8 (Miller 1999; Miller et al 1999) is a product of Eidactics.

KKD: none

ABS: Scott AB (2009). Medical Treatment of Muscles by Exposure to Anesthetic Drugs. Patent US 7,632,848 B1, filed 2007.10.04, issued 2009.12.15.

Scott AB (2012). Method of changing muscle lengths with anesthetic drugs. Patent US 8,193,220 B1, filed 2009.08.20, issued 2012.06.05.



## Abstract

*Purpose*: To report the magnitude and stability of corrections in comitant horizontal strabismus achieved by injecting bupivacaine (BPX, optionally with epinephrine) and botulinum A toxin (BTXA) into extraocular muscles of alert adult subjects with electromyographic (EMG) guidance.

*Subjects & Methods*: Fifty-five adult comitant horizontal strabismus patients participated in a prospective observational clinical series. Twenty-nine previously had 1 or more unsuccessful strabismus surgeries; 4 had had other orbital surgeries. Thirty-one patients with esodeviations received BPX injections in a lateral rectus muscle, some with BTXA in the medial rectus. Twenty-four patients with exodeviations received BPX in a medial rectus, some with BTXA in the lateral rectus. A second treatment (BPX, BTXA, or both) was given to 27 patients who had residual strabismus after the first treatment. Five patients required additional injections. Clinical alignment was measured at 6 mo, 1 yr, 2 yrs, 3 yrs, 4 yrs, and 5 yrs after treatment, with mean followup of 28 mo.

*Results*: On average, misalignment of 23.8$^{\Delta}$ (13.4°) was reduced at 28 mo by 16.0$^{\Delta}$ (9.1°), with successful outcomes (residual deviations ≤10$^{\Delta}$) in 56% of patients. Sixty-six percent of patients with initial misalignments ≤25$^{\Delta}$ enjoyed successful outcomes, with corrections averaging 13.2$^{\Delta}$ (7.5°), and 40% of patients with larger misalignments had successful outcomes, with corrections averaging 20.9$^{\Delta}$ (11.8°). Corrected alignments were stable over followups as long as 5 yrs.

*Conclusions*: Injection treatments resulted in stable, clinically significant corrections in comitant horizontal strabismus, providing low-cost alternatives to incisional strabismus surgery, particularly where it is desirable to minimize surgical anesthesia and avoid extraocular scarring.

# Introduction

Inadvertent injection into extraocular muscles of the amino amide anesthetic bupivacaine (BPX) frequently causes strabismus (Rainin and Carlson 1985). We showed that BPX injection could be used to correct strabismus by strengthening and shortening muscles (Scott, Alexander et al. 2007, Scott, Miller et al. 2009), and also described the use of botulinum type A toxin (BTXA) injection into the antagonist to reduce stretch of the BPX-injected muscle, allowing it to rebuild at reduced length. Corrections with combined BPX-BTXA treatment are about twice those with BPX alone (Scott, Miller et al. 2009). Using 3D reconstruction of magnetic resonance images (MRI), we found that BPX injection resulted in modest increases in muscle size, which unexpectedly decayed to preinjection values over about a year, while alignment remained stable (Miller, Scott et al. 2013).

The present study was a prospective observational clinical series, that included patients with varying diagnoses and treatment histories, in which treatment parameters were continually refined, as we learned how best to suit different deviations and patients. Our data are therefore more complex than in a controlled study, and high variability makes it difficult to demonstrate statistically significant effects. But, where significant effects are found, they tend to be larger and are generalizable to a larger population and wider range of treatment parameters than would be the case in a tightly controlled study (Schwartz and Lellouch 1967).

We here report alignment outcomes with up to 5 year followups in 55 consecutive cases of comitant horizontal strabismus, describe the use of agents in addition to BPX, and discuss indications for injection treatment.

# Subjects & Methods

## Patients

All experimental procedures were approved by IRBs of California Pacific Medical Center or the Smith-Kettlewell Eye Research Institute and followed regulations of the US Health Insurance Portability and Accountability Act of 1996. We offered pharmacologic injections as alternative treatments to all adult patients requesting correction of comitant horizontal strabismus. We did not emphasize cost, but some patients may have selected injection because it was without cost. Those who understood the experimental nature of the treatment and wished to participate gave written consent. Patients were excluded from the study if there was evidence of paresis, atrophy, mechanical restriction, or systemic disease that might impact extraocular muscle physiology. We did not otherwise exclude patients who had previous strabismus or other orbital surgery.

We were interested in stable, clinically useful treatment effects, and because both BPX and BTXA have transient effects, we included only patients who returned for 6 mo and later followups, at which time we could be confident that all transient effects had dissipated. Eleven patients were initially enrolled but lost to followup, and were therefore removed from the study. Of these, 2 presenting with exotropias of 20-30$^{\Delta}$ (11.3-16.7°) had shown no improvement 2 mo after a single treatment, and opted for surgery. Six had residual deviations $\leq$10$^{\Delta}$, and 2 were overcorrected from exotropia to esotropia, at 1-4 mo. One patient did not return after injection.

Thus, there were 55 study patients. Twenty-nine (53%) had 1 or more prior unsuccessful surgical attempts to correct their strabismus (a total of more than 50 surgeries), and 4 had had other prior orbital surgeries (*Appendix Table A1,* patients 32, 39, 41 & 52). Patients received BPX injections in one horizontal muscle, some with added epinephrine or BTXA injections in the antagonist. A second treatment was given to 27 patients who had residual strabismus after the first: either BPX (7), BTXA (3), or both (17). Five patients required further treatments. In 4 patients, BTXA was injected in the muscle previously treated with BPX to redress an overcorrection.

## Dosages

Decisions concerning BPX dose and use of adjuvants were made clinically, using stronger treatments (higher concentrations, greater volumes, and adjuvants) for larger deviations. MRI data collected immediately after injection (Miller, Scott et al. 2013) showed that 3.0 mL filled a horizontal rectus muscle. A few earlier injections were larger. Smaller volumes were used for smaller deviations. We used BPX concentrations 0.75-3.0 g/dL (Leiter's Rx Compounding, San Jose, CA), with lower concentrations for smaller deviations, or simply consequent to dilution by epinephrine 1:100,000. Where alignment improved, but not as much as desired, an additional, usually stronger, treatment was given. On average, the BPX dose per injection was 56 mg (s.d. 24).

BPX is cardiotoxic at doses above 1.5 mg/kg IV, although such doses are frequently given for spinal, urologic, and pelvic anesthesia. Toxicity is much lower for injections into muscles or other tissues, and it is essential that injection is not intravascular.

For most recent injections, BPX was combined with epinephrine on the idea that vasoconstriction would prolong tissue exposure, or with epinephrine and lidocaine. Lidocaine alone shows little myotoxicity in eye muscles (Magoon, Cruciger et al. 1982), so the effect of this addition is ascribed to the epinephrine content.

For larger deviations we used BTXA in the antagonist, an average of 3.1u (s.d. 1.6) per injection. These modest doses resulted in mild paresis lasting about a month.

Details of each treatment are given in *Appendix Table A1*.

## EMG-Guided Injections

Prior to injection, we instilled several drops of proparacaine 0.5% to reduce discomfort, and a drop of vasoconstrictor (e.g., brimonidine tartrate 0.1%). We optimized needle placement in the target muscle by electromyography (EMG) recorded at the tip of the injection needle as awake patients made voluntary gaze shifts.

Unlike BTXA, a large molecule that slowly diffuses to its sites of action at neuromuscular junctions, BPX is a small molecule which acts on myofibers themselves, and must achieve direct contact throughout the muscle before it is removed by absorption into the bloodstream (Park, Park et al. 2004). We therefore sought to broaden exposure by injecting most of the BPX in the posterior third and the remainder in the middle of the muscle, withdrawing the needle slowly to allow anterior spread along the needle track.

Bupivacaine myotoxicity can cause redness and swelling from muscle necrosis for a couple of days. Oral prednisone 40 mg at time of treatment and 30 mg/day for the 2 next days was given to a few patients who received bupivacaine doses over 60 mg, but its effectiveness was not measured.

## Alignment Measurement

Eye alignment was measured using prism-cover tests with a viewing distance of 3 m, and estimated by prism and corneal reflex for patients without steady central fixation. Alignment was measured before injection and as close as possible to predetermined 6 mo, 1 yr, 2 yr, 3 yr, 4 yr, and 5 yr followup times.

# Results

## Corrections and Their Stability

*Table 1* gives mean presenting deviations and corrections for all 55 patients. At their most recent examinations, an average of 28 mo after final treatments, initial misalignments of 23.8Δ (13.4°) were reduced by 16.0Δ (9.1°) with successful outcomes (residual deviations ≤10Δ) in 56% of patients. On average, 53% of the presenting deviation was corrected.

Seventeen patients (31%) had successful outcomes after 1 treatment, and 30 (55%) after 1 or 2 treatments. Five (9%) required more than 2 treatments.

| | Number of Treatments | | | Strabismus Type | | Previous Strabismus Surgery? | |
|---|---|---|---|---|---|---|---|
| | Only 1 | 1 or 2 | All | Eso | eXo | Yes | No |
| Initial Deviation | 22.9Δ (12.9°) | 23.6Δ (13.3°) | 23.8Δ (13.4°) | 21.0Δ (11.9°) | 27.6Δ (15.4°) | 20.1Δ (11.4°) | 27.9Δ (15.6°) |
| t-test, 2 tail (p) | | | | 0.03 | | 0.01 | |
| Absolute Correction | 15.4Δ (9.0°) | 14.6Δ (8.3°) | 16.0Δ (9.1°) | 13.0Δ (7.4°) | 19.8Δ (11.2°) | 14.2Δ (8.1°) | 18.0Δ (10.2°) |
| t-test, 2 tail (p) | <0.0001 | <0.0001 | <0.0001 | 0.06 | | 0.30 | |
| Relative Correction | 61% | 55% | 53% | 54% | 51% | 51% | 55% |
| t-test, 2 tail (p) | <0.0001 | <0.0001 | <0.0001 | 0.8 | | 0.7 | |
| Residual Deviation ≤10Δ | 31% (17) | 55% (30) | 56% (31) | 68% | 42% | 62% | 46% |
| t-test, 2 tail (p) | <0.0001 | <0.0001 | <0.0001 | 0.2 | | 0.6 | |
| Number of Patients | 55 | | | 31 | 24 | 29 | 26 |

***Table 1: Average Results at Most Recent Followup.*** *an average of 28 mo after the final treatment. Relative Correction is with respect to orthophoria. The 3 groups under Number of Treatments are cumulative (left to right); for each group, the percent of patients with successful outcomes is relative to the total number of patients in the study, and statistics test differences from zero. For "Strabismus Type" and "Previous Surgery?", subgroups are mutually exclusive and statistics test differences between the subgroups.*

| Initial Deviation Group | Initial Deviation | Number of treatments | BPX Cumulative Dose (mg) | BTXA Injection *(% patients)* | BTXA Cumulative Dose (u) | Absolute Correction | Relative Correction *(% desired)* | Residual Deviation ≤10Δ (% patients) | Number of Patients |
|---|---|---|---|---|---|---|---|---|---|
| ≤25Δ | 16.9Δ (9.6°) | 1.7 | 68 | 63 | 1.9 | 13.2Δ (7.5°) | 52 | 66 | 35 |
| >25Δ | 36.6Δ (20.1°) | 1.9 | 104 | 100 | 6.5 | 20.9Δ (11.8°) | 55 | 40 | 20 |
| t-Test (p) | | 0.2 | 0.005 | | 0.003 | 0.03 | 0.4 | | |

***Table 2: Small & Large Misalignments - Treatments and Outcomes.*** *Most recent available examination data are shown. Treatments include BPX, BTXA, and BPX-BTXA injections.*

For the subset of treatments that included both BPX and BTXA, the absolute correction for first treatments averaged 15.3Δ (8.7°), and that for 2nd treatments averaged 15.1Δ (8.6°).

Thirty-one patients had presented with esodeviations and 24 with exodeviations. There were no statistically significant differences on any outcome measure for esodeviations compared to exodeviations. The trend to larger absolute corrections for exodeviations is explained by larger initial deviations, and belied by the smaller percentage of patients with successful outcomes.

*Table 2* compares treatments and outcomes for "small" (≤25Δ) and "large" (>25Δ) presenting misalignments, which differed in average size by a factor of ~2. Small deviations tended to require fewer treatments, but the difference was not statistically significant. The total amount of BPX used with the large-deviation group was about 50% greater. BPX corrects larger misalignments with the help of BTXA in the antagonist muscle (Scott, Miller et al. 2009), and all patients in the large-misalignment group received this combined treatment, with an average total dose of 6.5u, compared to 63% of those in the small-misalignment group, with an average dose of 1.9u.

Absolute corrections of large deviations were 57% greater than small deviations, although only 40% of the former had successful outcomes, compared to 66% of the latter.

F*igure 1* shows the time course of alignment correction by separating patients into cohorts according to length of followup, so trends are not distorted by patients missing exams or leaving the study. It is clear that alignment corrections were quite stable, remarkably so after two years.

Six study patients had subsequent strabismus surgery.

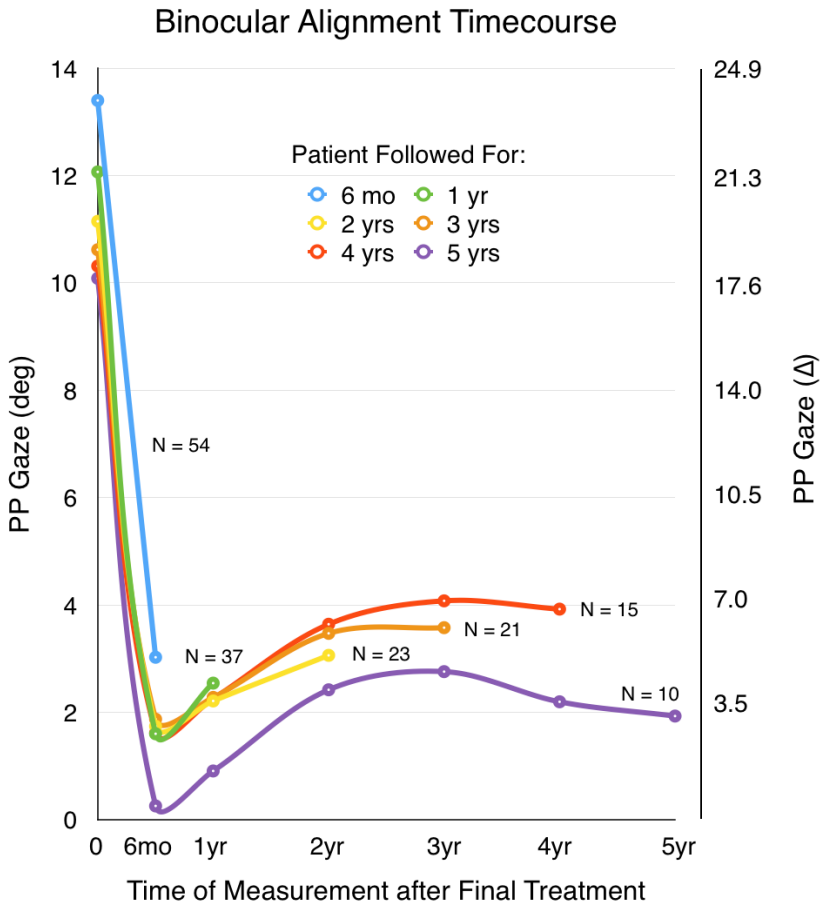


***Figure 1: Binocular Alignment Time-course.*** *Primary position gaze alignment (PP Gaze) is shown with patients grouped in cohorts according to how long we were able to follow them. The number of patients in each cohort is given by the label near its color-coded curve. Followups are measured from the time of the final treatment. (All 55 patients had initial alignment measures; one missed the 6 mo, measurement, but was measured at 1 yr)*

## Clinical Notes

Within minutes of a successful injection, and lasting for about a day, the anesthetic action of BPX blocks the motor nerve. Marked muscle weakness then results from myofibrillar destruction, with some inflammation related to muscle fiber necrosis, both of which diminish in the succeeding week. Rebuilding over 3-4 weeks results in progressive improvement in eye alignment. BTXA takes effect on day 2-3, so agonist and antagonist are typically about equally weakened, and eye alignment is not greatly changed for the first week or two.

Patient ID 13 (*Table A1*) received the highest dose we used, 120 mg BPX to the medial rectus. The area was swollen and chemotic for several days, and an area of conjunctival thickening over the medial rectus remains after 5 years. We subsequently limited BPX dose to 90 mg, and no enduring tissue change has occurred in any other case. There were no instances of globe perforation, optic nerve damage, or vision loss from EMG-guided BPX injection, and no instances of systemic toxicity.

# Discussion

## Strabismus Correction

In the present study we achieved absolute corrections 52% larger (16.0Δ, 9.1°) than previously (Miller, Scott et al. 2013) in patients with similar initial misalignments (23.8Δ, 13.4°). We attribute these improved outcomes to larger BPX doses, combination of BPX with epinephrine, and larger BTXA doses. The enhanced effect is most remarkable for the group of patients with initial misalignment >25Δ, where corrections averaged 20.9Δ (11.8°). We obtained clinically significant improvements with misalignments up to 50Δ, and demonstrated stability for as long as 5 years.

Most of our patients (56%) enjoyed successful outcomes. Success rates for incisional surgery in adults have been

estimated at 68-85% (Mills, Coats et al.), though generally with shorter followups, varying criteria of success, and in populations that do not include the challenging cases in our study.

For small misalignments, our initial doses were intentionally small to avoid over-correction, which probably contributed to the re-injection rate in those cases.

Differences in surgical outcomes for esodeviations and exodeviations are frequently reported, and we anticipated some such differences with injection treatment, perhaps because of the different paths and shapes of lateral and medial rectus muscles, but none were found. Still, this might be dependent on injection technique, and differences might emerge in other hands.

## Adjuvants

The vasoconstricting action of epinephrine may increase BPX effectiveness by prolonging its contact with muscle tissue. Patients receiving BPX with epinephrine enjoyed larger corrections, but we cannot conclude this was an effect of the adjuvant because these patients also got higher doses of BPX and BTXA.

## When Should Injection Treatment Be Considered?

Injection treatment is a low-cost office procedure that does not require general anesthesia in cooperative adults. Because there is no incisional approach or tissue dissection, it does not result in the scarring consequent to conventional surgery, and if therapeutic goals are not achieved with a single injection, additional injections or surgical treatments can readily be given. In our patients who subsequently had surgery, we observed no differences between injected and uninjected muscles and surrounding tissues.

Conversely, our results injecting untreated muscles were similar to those with muscles previously injected or operated on. Twenty nine of our study patients, had prior failed strabismus surgeries, and four more presented with strabismus secondary to retinal or glaucoma surgery. The outcomes from injection in these cases, however, were no less successful than cases without prior surgery. Therefore, BPX treatment may be particularly useful where previous orbital procedures have left adhesions and fibroses that complicate surgical approach, as when a muscle is incorporated in the capsule surrounding a scleral buckle or glaucoma drainage device. Injection treatment would probably not be useful with significant mechanical restriction, and such patients were excluded from the present study.

Injection volume influences the amount of muscle tissue exposed, and BPX concentration affects myotoxicity. At present, based on our results and experience, we offer the following guidelines for injection treatment of comitant strabismus (*Table 3)*.

Given an upper limit of about 90 mg of BPX in a single injection, large misalignments will often require 2 treatments. Our injection dosages in the present study for small deviations were probably not optimal. Of our 6 overcorrected patients, most had small initial deviations (*Table A1*). Recent experience suggests that smaller BPX volumes may confer greater control in these cases, but correction by adjustable surgical techniques may be preferred where even a small over-correction would result in diplopia.

| Initial Deviation (Δ) | BPX | | | BTXA (u) |
|---|---|---|---|---|
| | Vol (mL) | Conc (%) | Epinephrine (μg) | |
| 6 - 12 | 1.25 - 2.00 | 1.50 - 2.50 | 0 | 0.0 |
| 13 - 30 | 2.50 - 3.00 | 1.50 - 2.75 | 5 - 10 | 1.5 - 2.5 |
| > 30 | 3.00 | 3.00 | 5 - 10 | 2.5 - 5.0 |

***Table 3: Injection Treatment Guidelines.***

BPX treatment should also be considered to correct post-operative deviations in patients with good potential for binocularity who wish to avoid reoperation.

Two advantages of pharmacologic treatment have particular currency.

### Injections in Children

Most strabismus patients are children, in whom correction can facilitate normal visual and social development. However, there is concern that such general anesthesia as required for conventional surgery may damage the developing brain, and it has been recommended that anesthetic procedures in young children be considered carefully (eg, SmartTots 2015) and kept as brief as possible (eg, Good 2014). It would therefore be extremely valuable to have a strabismus treatment option for children that required only very brief anesthesia.

In cooperative adults, pharmacologic injections can be guided by EMG. Children, however, would need to be briefly anesthetized, making it difficult to record movement-related EMG. BTXA can be injected near the insertional end of a muscle without guidance (Mendonca, Cronemberger et al. 2005) and allowed to diffuse posteriorly, but BPX must be injected throughout the body of the muscle (Park, Park et al. 2004). We are therefore developing a method of targeting eye muscle injections using electrical stimulation under anesthesia, and are also planning a trial in children using ketamine, which does not abolish the EMG.

Children who have strabismus surgery often require reoperations, made more difficult by scarring, which would be minimal or absent if initial treatment were by injection.

It is currently unknown whether children respond more or less strongly to BPX injection than adults.

### Medical Economics

BPX injection treatment for cooperative adults currently requires an average of 2 office visits with an ophthalmologist, each about 15 min, compared to traditional strabismus surgery, which requires an ophthalmologist, an anesthetist, and a staffed operating room for perhaps an hour, along with time in a recovery room. With broadening coverage by government and other large institutions, pressures to reduce costs can be expected to increase.

## Pragmatic vs Explanatory Studies

In terms introduced by Schwartz and Lellouch (1967), the present study was more *pragmatic* than *explanatory*. Pragmatic studies intend to be more relevant to real-world clinical decisions, with typical patients, settings, and treatments. Explanatory studies, in contrast, test hypotheses about underlying biological processes by tightly controlling these factors to maximize contrasts. Consequently, much remains to be discovered about the mechanisms involved in BPX treatment.

## Physiological Mechanisms

Little is known about the mechanism of size increase in the weeks immediately following BPX injection. One possibility is that general myofiber destruction elicits satellite cell-mediated regeneration in which replacement fibers tend to be larger than those replaced (Rosenblatt and Woods 1992). Another is that small, weak fibers (having large surfaces vulnerable to BPX attack relative to small volumes in which to cope with the metabolic consequences) are particularly susceptible to BPX. Finally, it is possible for myofibers to be damaged without being destroyed (Hall-Craggs 1974), in which case satellite cells may add myonuclei to repair the damage, creating a cell with a permanent tendency to hypertrophy (Bruusgaard, Johansen et al. 2010). None of these mechanisms are mutually exclusive, and different injection formulations might favor one or the other.

We are currently developing techniques to measure sarcolemmal disruption, and determine the effects of BPX injection on fiber size distribution.

## Biomechanical Mechanisms

We previously reported that BPX injection resulted in modest increases in muscle size (6.6% in volume and 8.5% in maximum crossection), but that muscles gradually returned to pre-injection sizes, while alignment corrections remained stable (Miller, Scott et al. 2013). What, then, is the relationship between muscle force and eye alignment?

It is possible that BPX increases intrinsic muscle stiffness by adding connective tissue during regeneration (Rosenblatt and Woods 1992), and indeed, small stiffness increases in BPX injected muscles have been measured (Han, Kim et al. 2004). However, simulation with Orbit™ 1.8 (Miller 1999, Miller, Pavlovski et al. 1999) makes clear something first pointed out by Robinson (1975), that force changes have little effect on alignment, compared to similar fractional changes in muscle length.

*Figure 2* compares effects on primary position gaze of increases in force (including both innervation-related contractile force and stiffness-related elastic force) of a BPX-injected muscle, compared to length-adaptive changes in LR and MR, resulting from serial sarcomere addition and deletion (Scott 1994, Goldspink, Cox et al. 1995). It can be seen that changes in the latter have far greater effects on gaze.

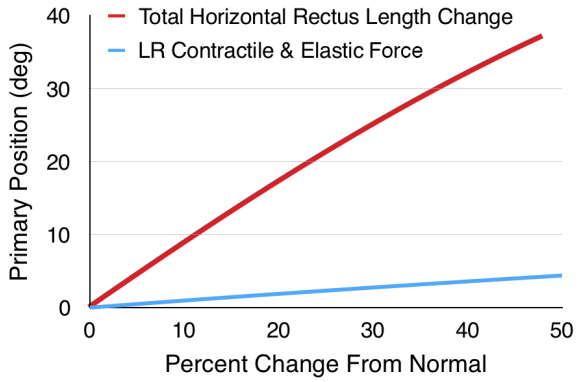


***Figure 2: Alignment Is More Sensitive to Muscle Length Than to Force.*** *Effects on primary position of increases in force of a BPX-injected muscle, compared to length-adaptive changes in LR and MR, as predicted by Orbit™ 1.8.*

This means that only dramatic stiffness increases, such as those characteristic of fibrotic syndromes, could themselves account for the large alignment changes we achieved, but because such nonlinear restrictive pathologies would be evident in gaze limitations, which were not observed, stiffness changes are an implausible explanation of the stable alignment changes we achieved.

We hypothesize that BPX-induced hypertrophy rotates the eye, causing the injected muscle to traverse a shorter path, and its antagonist a longer path, gradually resulting in adaptive length changes, with the BPX-injected muscle becoming shorter and its antagonist longer. As length changes proceed, and nonmuscular tissues relax to the new alignment, loads on the BPX-injected muscle decrease, allowing its size to down-regulate towards the pre-injection values we observed.

Thus, following transient increases in muscle size, BPX treatment results in stable changes in muscle lengths, without recession, resection, or other compensatory damage to extraocular biomechanics.

Histological and biomechanical studies are underway to test these ideas.

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## Appendix

| Patient | | | Injections | | | | | | | Outcome | | Prev Rprt ? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Agonist | | | | | Antagonist | | | | |
| ID | Age (years) | Initial Deviation (Δ) | Muscle | Volume (mL) | BPX | | Epi-nephrine | BTX | | Final Deviation (Δ) | Days After Final Treatment | |
| | | | | | Conc (%) | Dose (mg) | Dose (μg) | Muscle | Dose (u) | | | |
| 1 | 72.3 | ET 15 | RLR | 4.5 | 0.75 | 34 | | | | 0 | 2127 | √ |
| 2 | 52.7 | ET 9 | RLR | 1 | 3 | 30 | | | | 0 | 1904 | √ |
| 3 | 41.8 | ET 25 | RLR | 1 | 3 | 30 | | | | ET 7 | 1658 | √ |
| | 42.2 | | RLR | 3 | 1.5 | 45 | | | | | | |
| 4 | 70.9 | ET 16 | LLR | 1.5 | 0.75 | 11 | | | | ET 14 | 1148 | √ |
| | 72.6 | | LLR | 4.5 | 0.75 | 34 | | LMR | 1.5 | | | |
| 5 | 38.7 | ET 10 | LLR | 1 | 0.75 | 8 | | | | ET 3 | 2470 | √ |
| | 39.1 | | LLR | 3 | 1.5 | 45 | | | | | | |
| 6 | 33.9 | ET 14 | RLR | 3 | 1.5 | 45 | | | | ET 9 | 1243 | √ |
| | 35.3 | | RLR | 4 | 3 | 120 | | RMR | 1.5 | | | |
| 7 | 52.7 | XT 16 | LMR | 3 | 3 | 90 | | LLR | 3 | XT 1 | 2231 | √ |
| 8 | 74.4 | XT 20 | LMR | 4 | 0.75 | 30 | | LLR | 2 | 0 | 1867 | √ |
| 9 | 71.3 | XT 40 | RMR | 4 | 0.75 | 30 | | RLR | 5 | XT 18 | 247 | √ |
| 10 | 77.2 | ET 30 | RLR | 4.5 | 0.75 | 34 | | RMR | 2.75 | ET 35 | 246 | √ |
| | 80.2 | | RLR | 3 | 2 | 60 | | RMR | 1.5 | | | |
| 11 | 48.0 | XT 12 | RMR | 4.5 | 0.75 | 34 | | | | XT 8 | 1517 | √ |
| | 48.7 | | RMR | 2.75 | 3 | 83 | | | | | | |
| 12 | 62.8 | ET 10 | LLR | 4 | 0.75 | 30 | | | | ET 5 | 1954 | √ |
| | 63.2 | | LLR | 3.5 | 0.75 | 26 | | | | | | |
| 13 | 26.3 | XT 40 | RMR | 4 | 3 | 120 | | RLR | 4 | XT 14 | 1824 | |
| | 26.3 | | | | | | | RLR | 7.5 | | | |
| 14 | 38.6 | XT 50 | LMR | 4 | 3 | 120 | | LLR | 4 | ET12* | 840 | √ |
| | 38.8 | | LMR | 3.5 | 3 | 105 | | LLR | 5 | | | |
| | 38.8 | | | | | | | LLR | 4 | | | |
| | 38.9 | | | | | | | LMR | 2 | | | |
| | 39.1 | | | | | | | LMR | 4 | | | |
| 15 | 51.7 | ET 25 | | | | | | RMR | 2.5 | 0 | 2136 | √ |
| | 51.7 | | | | | | | RMR | 3 | | | |
| | 52.1 | | RLR | 3 | 0.75 | 23 | | RMR | 3 | | | |
| | 52.3 | | RLR | 3 | 0.75 | 23 | | RMR | 3 | | | |
| | 52.4 | | | | | | | RLR | 2.5 | | | |
| 16 | 48.9 | XT 25 | RMR | 3 | 0.75 | 23 | | RLR | 1.25 | XT 25 | 275 | √ |
| | 49.2 | | RMR | 3 | 1.5 | 45 | | | | | | |
| 17 | 71.3 | ET 40 | LLR | 3 | 1.5 | 45 | | LMR | 1.5 | 0 | 1213 | √ |
| | 72.0 | | LLR | 3.25 | 3 | 98 | | LMR | 4 | | | |
| 18 | 32.7 | ET 14 | RLR | 3 | 0.75 | 23 | | | | ET 12 | 411 | √ |
| 19 | 27.2 | XT 40 | RMR | 3 | 2.5 | 75 | | RLR | 5 | XT 40 | 229 | √ |
| 20 | 20.2 | ET 23 | LLR | 3 | 1.5 | 45 | | LMR | 2 | ET 4 | 2003 | √ |
| 21 | 54.4 | ET 30 | LLR | 3 | 2.5 | 75 | | LMR | 2 | 0 | 204 | √ |
| | 56.6 | | LLR | 2.75 | 2.5 | 69 | | LMR | 2.5 | | | |
| 22 | 32.6 | ET 12 | LLR | 1.75 | 2 | 35 | 17.5 | LMR | 1 | ET 9 | 415 | |
| | 32.6 | | LLR | 2.5 | 2.5 | 63 | | LMR | 2 | | | |
| 23 | 29.0 | ET 12 | RLR | 3 | 1.5 | 45 | | | | ET 18 | 1487 | √ |
| | 29.1 | | RLR | 3.5 | 3 | 105 | | RMR | 1.5 | | | |
| 24 | 58.2 | ET 12 | RLR | 3 | 2 | 60 | | | | 0 | 1423 | √ |
| 25 | 50.6 | XT 35 | | | | | | LLR | 3 | XT 25 | 258 | √ |
| | 50.6 | | | | | | | LLR | 6 | | | |
| | 50.9 | | LMR | 3 | 1.5 | 45 | | LLR | 5 | | | |
| | 51.5 | | LMR | 3 | 2 | 60 | | LLR | 5 | | | |
| | 51.7 | | LMR | 2.5 | 3 | 75 | | LLR | 5 | | | |
| | 51.7 | | | | | | | LLR | 8 | | | |

| Patient | | | Injections | | | | | | | Outcome | | Prev Rprt ? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Agonist | | | | | Antagonist | | | | |
| ID | Age (years) | Initial Deviation (Δ) | Muscle | Volume (mL) | BPX | | Epi-nephrine | BTX | | Final Deviation (Δ) | Days After Final Treatment | |
| | | | | | Conc (%) | Dose (mg) | Dose (μg) | Muscle | Dose (u) | | | |
| 26 | 58.6 | ET 12 | RLR | 3.1 | 2 | 62 | | | | ET 2 | 1799 | √ |
| 27 | 70.3 | ET 12 | LLR | 3.25 | 0.75 | 24 | | | | XT 7* | 1082 | |
| 28 | 74.2 | ET 35 | LLR | 4 | 1.5 | 60 | | LMR | 1.25 | ET 30 | 1617 | √ |
| | 74.5 | | LLR | 3 | 2 | 60 | | LMR | 2.5 | | | |
| 29 | 75.3 | XT 40 | RMR | 3 | 2 | 60 | | RLR | 1.25 | XT 4 | 411 | √ |
| | 77.3 | | LMR | 3 | 2.5 | 75 | 2 | LLR | 1.5 | | | |
| 30 | 56.3 | XT 10 | RMR | 3 | 2 | 60 | | | | ET 15* | 734 | |
| | 56.4 | | | | | | | RLR | 5 | | | |
| | 58.6 | | RMR | 2.5 | 2 | 50 | 17.5 | | | | | |
| | 59.2 | | | | | | | RMR | 3 | | | |
| | 60.1 | | | | | | | RMR | 3 | | | |
| 31 | 67.5 | XT 30 | LMR | 3 | 2.5 | 75 | | LLR | 2.5 | XT 2 | 528 | √ |
| 32 | 62.6 | ET 15 | RLR | 3 | 2 | 60 | | | | ET 9 | 1266 | √ |
| | 62.8 | | RLR | 3 | 2.5 | 75 | | RMR | 4 | | | |
| 33 | 27.4 | ET 18 | RLR | 3 | 2.5 | 75 | | RMR | 1 | ET 3 | 461 | |
| 34 | 65.8 | XT 10 | LMR | 2 | 1.5 | 30 | | | | ET 11* | 295 | |
| 35 | 44.2 | XT 16 | LMR | 3 | 1.5 | 45 | 15 | | | XT 16 | 469 | |
| | 44.3 | | RMR | 3 | 2.5 | 75 | | | | | | |
| 36 | 45.6 | ET 12 | RLR | 2 | 1.5 | 30 | | | | ET 4 | 756 | |
| 37 | 70.2 | XT 40 | LMR | 3 | 2.5 | 75 | 30 | LLR | 2.5 | XT 4 | 215 | |
| | 71.7 | | LMR | 3 | 2 | 60 | 10 | LLR | 4 | | | |
| 38 | 33.0 | XT 45 | LMR | 2.75 | 2.5 | 69 | 2.75 | LLR | 4 | XT 25 | 251 | |
| | 34.1 | | LMR | 3 | 2 | 60 | 10 | LLR | 5 | | | |
| 39 | 62.7 | XT 25 | RMR | 2 | 1.5 | 30 | 10 | RLR | 2 | 0 | 992 | |
| | 62.7 | | | | | | | RLR | 5 | | | |
| 40 | 60.2 | ET 35 | RLR | 2.5 | 2 | 50 | 2 | RMR | 2 | ET 35 | 632 | |
| 41 | 55.5 | XT 18 | RMR | 3 | 2 | 60 | 3 | RLR | 2.5 | 0 | 203 | |
| 42 | 28.2 | XT 25 | RMR | 3 | 2 | 60 | 3 | RLR | 2.5 | 0 | 510 | |
| | 28.4 | | LMR | 2.5 | 3 | 75 | | RLR | 2 | | | |
| 43 | 23.4 | ET 30 | LLR | 3 | 2 | 60 | 3 | LMR | 1.5 | ET 10 | 169 | |
| 44 | 75.8 | XT 40 | LMR | 3 | 2.5 | 75 | 5 | LLR | 5 | XT 10 | 464 | |
| 45 | 82.7 | XT 25 | LMR | 3 | 2 | 60 | 10 | LLR | 2.5 | XT 13 | 444 | |
| 46 | 34.9 | ET 30 | RLR | 3 | 2.5 | 75 | 5 | RMR | 5 | ET 12 | 182 | |
| | 35.6 | | RLR | 2 | 3 | 60 | | RMR | 1.25 | | | |
| 47 | 35.0 | ET 18 | LLR | 2.5 | 2 | 50 | 10 | LMR | 1.5 | ET 18 | 272 | |
| 48 | 64.0 | XT 14 | RMR | 2.75 | 2.5 | 69 | 15 | | | ET 12* | 448 | |
| | 64.1 | | | | | | | RLR | 1.25 | | | |
| | 64.6 | | | | | | | RMR | 2 | | | |
| 49 | 47.0 | ET 25 | RLR | 2.5 | 1.5 | 38 | 12.5 | RMR | 2 | 0 | 258 | |
| 50 | 23.8 | XT 30 | LMR | 2 | 2 | 40 | | LLR | 1.25 | XT 14 | 350 | |
| 51 | 39.7 | ET 33 | LLR | 3 | 2 | 60 | 10 | LMR | 4 | 0 | 440 | |
| 52 | 65.5 | XT 25 | LMR | 3 | 2.1 | 62 | 5 | LLR | 2.5 | XT 14 | 316 | |
| 53 | 23.1 | ET 20 | LLR | 3 | 2 | 60 | 10 | LMR | 2 | XT 20* | 196 | |
| 54 | 25.8 | ET 40 | LLR | 3 | 2.1 | 62 | 2.5 | LMR | 5 | ET 33 | 154 | |
| 55 | 53.6 | ET 25 | RLR | 3 | 2 | 60 | 5 | RMR | 2.5 | 0 | 176 | |

*Table A1: Patients, Treatments, and Outcomes. Each patient is listed by "ID", assigned in the order of enrollment in the study, with the "Age" at which treatment was provided, and the presenting or "Initial Deviation". The muscle receiving BPX is designated "Agonist", and the opposing muscle, "Antagonist" ("LLR" = left lateral rectus, "RLR" = right lateral rectus, "LMR" = left medial rectus, "RMR" = right medial rectus). "Volume" is the total volume of fluid injected, constituted as shown (blank cells mean "none"). "Outcome" is shown for each patient at the most recent followup exam; overcorrections are indicated with an "*" in the "Final Deviation" column. A "√" under "Prev Rprt" indicates early followup data that were previously reported.*