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Pharmacologic injection treatment of comitant strabismus

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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—A total of 55 adults with comitant horizontal strabismus participated in a prospective observational clinical series. Of these, 29 previously had undergone 1 or more unsuccessful strabismus surgeries; 4 had undergone other orbital surgeries. Thirty-one patients with esodeviations received BPX injections in a lateral rectus muscle, some with BTXA in the medial rectus; 24 patients with exodeviations received BPX in a medial rectus muscle, some with BTXA in the lateral rectus muscle. A second treatment (BPX, BTXA, or both) was administered to 27 patients who had residual strabismus after the first treatment. Five patients required additional injections. Clinical alignment was measured at 6 months and yearly thereafter through 5 years' follow-up, with mean follow-up of 28 months. A successful outcome was defined as residual deviation $\leq 10^\circ$.

Results—On average, presenting misalignment of 23.8° (13.4°) was reduced at 28 months by 16.0° (9.1°), with successful outcomes in 56% of patients. Of patients with initial misalignments $\leq 25^\circ$, 66% had successful outcomes, with corrections averaging 13.2° (7.5°); of patients with larger misalignments, 40% had successful outcomes, with corrections averaging 20.9° (11.8°). Corrected alignments were stable over follow-ups as long as 5 years.

Conclusions—Injection treatments resulted in stable, clinically significant corrections in comitant horizontal strabismus. Injection provides a low-cost alternative to incisional strabismus

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Orbit 1.8 (Miller 1999; Miller et al 1999) is a product of Eidactics. ABS holds the following patents: 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.

surgery, particularly where it is desirable to minimize surgical anesthesia and avoid extraocular scarring.

Inadvertent injection into extraocular muscles of the amino amide anesthetic bupivacaine (BPX) frequently causes strabismus.¹ We showed that BPX injection could be used to correct strabismus by strengthening and shortening muscles^{2,3} 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.⁴ Using 3D reconstructions 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.⁵

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.⁶ We report alignment outcomes with up to 5 years' follow-up in 55 consecutive cases of comitant horizontal strabismus, describe the use of agents in addition to BPX, and discuss indications for injection treatment.

Subjects and Methods

All experimental procedures were approved by the institutional review boards 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. Pharmacologic injections were offered 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 provided written consent. Patients with evidence of paresis, atrophy, mechanical restriction, or systemic disease that might affect extraocular muscle physiology were excluded; patients who had undergone previous strabismus or other orbital surgery were not otherwise excluded.

We sought to identify stable, clinically useful treatment effects, and because both BPX and BTXA have transient effects, we included only patients with at least 6 months' follow-up, at which time we could be confident that transient effects had dissipated. Eleven patients were initially enrolled but lost to follow-up and were therefore removed from the study. Of these, 2 who presented with exotropias of 20 -30 (11.3°-16.7°) had shown no improvement 2 months after a single treatment and opted for surgery. Six had residual deviations 10 , and 2 were overcorrected from exotropia to esotropia, at 1-4 months. One patient did not return after injection.

Thus there were 55 study patients, 29 with 1 or more prior unsuccessful surgical attempts to correct their strabismus (a total of more than 50 surgeries), and 4 who had undergone other prior orbital surgeries (Appendix A [e-only], 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 patients), BTXA (3), or both (17). Some patients required further treatments. In 4 patients, BTXA was injected in the muscle previously treated with BPX to redress an overcorrection.

Treatment success was defined as residual deviation $\leq 10^\circ$.

Decisions concerning BPX dose and use of adjuvants were made clinically: stronger treatments (higher concentrations, greater volumes, and adjuvants) were used for larger deviations. MRI data collected immediately after injection⁵ 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 of 0.75–3.0 g/dL (Leiter's R_X 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 administered. 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 assumption that vasoconstriction would prolong tissue exposure, or with epinephrine and lidocaine. Lidocaine alone shows little myotoxicity in eye muscles⁷; therefore, the effect of this addition is ascribed to the epinephrine content.

For larger deviations BTXA was injected into the antagonist, an average of 3.1u (s.d. 1.6) per injection. These modest doses resulted in mild paresis lasting about a month. The details of each treatment are provided in Appendix A.

Prior to injection, several drops of proparacaine 0.5% were instilled to reduce discomfort in addition to 1 drop of vasoconstrictor (eg, 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.⁸ 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 temporary redness and swelling from muscle necrosis. Oral prednisone 40 mg at the time of treatment and 30 mg/day for the 2 next days was given to patients who received bupivacaine doses over 60 mg, but its effectiveness was not measured.

Eye alignment was measured using prism cover testing 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 follow-up examinations at 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years.

Results

Corrections and their Stability

Table 1 provides the mean presenting deviations and corrections for all 55 study patients. At their most recent examinations, an average of 28 months after final treatments, initial misalignments of 23.8 (13.4°) were reduced by 16.0 (9.1°), with successful outcomes 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.

For the subset of treatments that included both BPX and BTXA, absolute corrections for first treatments averaged 15.3 (8.7°); for second treatments, 15.1 (8.6°).

Of the 55 patients, 31 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 (≤ 25°) and large (>25°) initial misalignments, which differed in average size by a factor of about 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,⁴ and all patients in the large-misalignment group received this combined treatment, with an average total dose of 6.5 u, compared to 63% of those in the small-misalignment group, with an average total dose of 1.9 u. 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.

Figure 1 shows the time course of alignment correction by separating patients into cohorts according to length of follow-up; trends are thus not distorted by patients missing examinations or leaving the study. It is clear that alignment corrections were quite stable, remarkably so after 2 years.

Six study patients had subsequent strabismus surgery.

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 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 1-2 weeks.

Patient 13 (Appendix A) received the highest dose we used, 120 mg BPX to the medial rectus muscle. The area was swollen and chemotic for several days, and an area of conjunctival thickening over the medial rectus remained at 5 years' follow-up. We subsequently limited BPX doses to 90 mg; no enduring tissue change was noted in any other case. There were no instances of globe perforation, optic nerve damage, or vision loss from EMG-guided BPX injection in this study. There were no instances of systemic toxicity.

Discussion

Strabismus Correction

In the present study we achieved corrections 52% larger (16° , 9.1°) than previously⁵ in patients with similar initial misalignments (23.8° , 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 $>25^\circ$, where corrections averaged 20.9° (11.8°). We obtained clinically significant improvements with misalignments up to 50° , 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%,⁹ though generally with shorter follow-ups, 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 overcorrection, which probably contributed to the reinjection rate in those cases.

Differences in surgical outcomes for eso- and exodeviations are frequently reported, and we anticipated some 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.

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

Treatment Considerations

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 are similar to those with previously injected or operated muscles. Twenty-nine of our study patients had prior failed strabismus surgeries, and 4 more presented with strabismus secondary to retinal or glaucoma surgery. The outcomes from injection in these cases 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. However, injection treatment would probably not be useful with significant mechanical restriction, and such patients were excluded from this study.

Injection volume influences the amount of muscle tissue exposed, and BPX concentration affects myotoxicity. Based on our results and experience, we offer the guidelines of Table 3 for injection treatment of comitant strabismus.

Given the upper limit of 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 (Appendix A). 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 overcorrection would result in diplopia.

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

Two advantages of pharmacologic treatment have particular currency, namely, treatment of pediatric patients and cost-effectiveness. Most strabismus patients are children, in whom correction can facilitate normal visual and social development. However, there is concern that the general anesthesia required for conventional surgery may damage the developing brain, and it has been recommended that anesthetic procedures in young children be considered carefully¹⁰ and kept as brief as possible.¹¹ 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 guidance¹² and allowed to diffuse posteriorly, but BPX must be injected throughout the body of the muscle.⁸ We are therefore developing a method of targeting eye muscle injections using electrical stimulation

under anesthesia, and are planning a trial in children using ketamine, which does not abolish the EMG.

Children who undergo 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.

BPX injection treatment for cooperative adults currently requires an average of 2 office visits with an ophthalmologist, each about 15 minutes, 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.

Physiological Mechanisms

Little is known about the mechanism of size increase in the weeks 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.¹³ 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,¹⁴ in which case satellite cells may add myonuclei to repair the damage, creating a cell with a permanent tendency to hypertrophy.¹⁵ 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 crosssection), but that muscles gradually returned to preinjection sizes, while alignment corrections remained stable.⁵ 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,¹³ and indeed, small stiffness increases in BPX injected muscles have been measured.¹⁶ However, simulation with Orbit 1.8^{17,18} makes clear something first pointed out by Robinson,¹⁹ 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 lateral rectus and medial rectus muscles, resulting from serial sarcomere addition and deletion.^{20,21} It can be seen that changes in the latter have far greater effects on gaze. 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 toward the preinjection 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG 1.

Binocular alignment time course. Primary position gaze alignment (PP gaze) is shown with patients grouped into 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. Follow-up times are measured from the time of the final treatment. (All 55 patients had initial alignment measures, and all but one had measurements at 6 months.)

FIG 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 lateral rectus and medial rectus muscles, as predicted by Orbit 1.8.

Table 1Average results at most recent follow-up, an average of 28 months after the final treatment^a

	No. treatments			Strabismus type		Previous strabismus surgery?	
	Only 1	1 or 2	All	Eso	Exo	Yes	No
Initial dev, PD (deg)	22.9 (12.9)	23.6 (13.3)	23.8 (13.4)	21.0 (11.9)	27.6 (15.4)	20.1 (11.4)	27.9 (15.6)
2 tailed <i>t</i> test, <i>P</i> value				0.03		0.01	
Absolute correction, PD (deg)	15.4 (9.0)	14.6 (8.3)	16.0 (9.1)	13.0 (7.4)	19.8 (11.2)	14.2 (8.1)	18.0 (10.2)
2 tailed <i>t</i> test, <i>P</i> value	<0.0001	<0.0001	<0.0001		0.06		0.30
Relative correction, %	61	55	53	54	51	51	55
2 tailed <i>t</i> test, <i>P</i> value	<0.0001	<0.0001	<0.0001	0.8		0.7	
Residual dev 10 PD, % (n)	31 (17)	55 (30)	56 (31)	68	42	62	46
2 tailed <i>t</i> test, <i>P</i> value	<0.0001	<0.0001	<0.0001		0.2		0.6
No. patients		55		31	24	29	26

Dev, deviation; *Eso*, esotropia; *Exo*, exotropia; *PD*, prism diopter.

^aThe 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.

Table 2Small and large misalignments treated with bupivacaine (BPX), botulinum A toxin (BTXA), or both^a

Initial deviation group	Initial deviation, PD (deg)	No. treatments	BPX cumulative dose, mg	BTXA injection (% patients)	BTXA cumulative dose (u)	Absolute correction, PD (%)	Relative correction (% desired)	Residual deviation 10 PD (% patients)	No. patients
25 PD	16.9 (9.6)	1.7	68	63	1.9	13.2 (7.5)	52	66	35
>25 PD	36.6 (20.1)	1.9	104	100	6.5	20.9 (11.8)	55	40	20
<i>t</i> test, <i>P</i> value		0.2	0.005		0.003	0.03	0.4		

PD, prism diopter.^aMost recent available examination data are shown.

Table 3

Injection treatment guidelines

Initial deviation, PD	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

BPX, bupivacaine; *BTXA*, botulinum A toxin; *Conc*, concentration; *PD*, prism diopter.