Bupivacaine injection of the lateral rectus muscle to treat esotropia

Alan B. Scott, MD, Joel M. Miller, PhD, and Kevin R. Shieh, BS

PURPOSE We report results of a pilot trial of bupivacaine injection into extraocular muscles as a method of enlarging and strengthening the muscles to treat strabismus.

METHODS Bupivacaine, in volumes from 1.0 to 4.5 mL and concentrations from 0.75% to 3.0%, was injected into 1 lateral rectus muscle in each of 6 patients with comitant esotropia with the use of the electrical activity recorded from the needle tip to guide injection. Magnetic resonance imaging was performed before and at intervals after injection to estimate changes in muscle size. Clinical measures of alignment were made before and at intervals after injection. Two patients required a second injection for adequate effect.

RESULTS Four patients showed improved eye alignment, averaging 12^{Δ}, measured an average of 367 days after the last injection (range, 244-540 days). Two patients were substantially unchanged. Alignment improvement for all 6 patients averaged 8^{Δ} (range, 0-14^{Δ}). Volumetric enlargement of the injected muscle, computed from magnetic resonance images, was 6.2% (range, –1.5% to 13.3%). There was a positive correlation between alignment change and muscle enlargement averaging 0.65. Injection caused a retrobulbar hemorrhage in an unchanged patient that cleared without affecting vision.

CONCLUSIONS Bupivacaine injection improved eye alignment in 4 of 6 esotropic patients. There was a positive correlation between improved eye alignment and increased muscle size. Clinical and laboratory studies are underway to determine optimal dosages, effects in other strabismus conditions, and differential effects of bupivacaine on contractile and elastic muscle components. (J AAPOS 2009;13:119-122)

In addition to its anesthetic effect, bupivacaine selectively damages striated muscle fibers, leaving supporting cellular structures, nerves, and satellite cells intact.[1-4] The damaged tissue releases growth factors such as mechano growth factor and insulin-like growth factor-IEa, which have autocrine function, causing satellite cells to proliferate and coalesce as new muscle fibers, thereby repairing the damage.[5,6] In the fast-twitch limb muscles of the rat, which resemble extraocular muscles, this process continues to hypertrophy.[7,8] Repeated injections give additional increases in muscle weight.[2] Some of the additional protein may not be contractile.[9] Reports of strabismus after exposure of eye muscles to bupivacaine given as retrobulbar anesthesia for cataract surgery emphasize a deviation of the eye into the field of action of the enlarged muscle,[10-12] implying increased contractility as well as increased stiffness. The present report follows-up our earlier reports of bupivacaine injection treatment in these cases.[13,14]

Author affiliations: The Smith-Kettlewell Eye Research Institute, San Francisco, California

Some of these data were reported in the Proceedings of the 31st Meeting of the European Strabismological Association, 2008.

Submitted May 5, 2008.

Revision accepted October 26, 2008.

Reprint requests: Alan B. Scott, MD, 2318 Fillmore Street, San Francisco, CA 94115 (email: abs@ski.org).

1091-8531/2009/$36.00 + 0

doi:10.1016/j.jaapos.2008.10.016

Methods

This study was approved by the Institutional Review Board of the Smith-Kettlewell Eye Research Institute and was performed in compliance with the United States Health Insurance Portability and Accountability Act. Eye alignment was measured by the use of standard clinical techniques, including the Hess screen; values reported are for patients fixing with their uninjected eyes in primary position at a distance of 3 m. Bupivacaine was injected into a lateral rectus muscle by using the electromyogram recorded from the needle tip to guide the location of the injection. A second bupivacaine injection was given in patients 3 and 5, who had had clinically insufficient alignment responses to the initial injection.

Magnetic resonance imaging (MRI) with a standard head coil was used to estimate muscle size. We obtained 3.0 mm thick T1 coronal slices separated by 0.5–1.0 mm gaps through both orbits, from the orbital apex to the equator of the eye, and similar axial slices through the horizontal recti. Scanning was performed before injection to establish baseline muscle sizes, about 20 minutes after injection to visualize the location of the injected fluid, at 30–60 days to show any changes in the muscles, and at intervals 3–6 months thereafter to show evolution of any changes.

ImageJ software (U.S. National Institutes of Health, 1997-2008, http://rsb.info.nih.gov/ij/index.html) was used to compare MR images and estimate muscle cross-sections and muscle

Table 1. Patient and treatment summary

Patient		Bupivacaine		Eye alignment change		
Patient no.	Age (years)	Concentration (%)	Volume (mL)	Total follow-up (days)	Per injection (PD)	Total (PD)
1	74	0.75	4.5	540	11	11
2	54	3.00	1.0	266	10	10
3, inj 1	43	3.00	1.0	161	10	14
3, inj 2		1.50	3.0	417	4	
4	72	0.75	1.5	517	2	2
5, inj 1	40	0.75	1.0	153	4	12
5, inj 2		1.50	3.0	244	8	
6	35	1.50	3.0	76	0	0
Mean					6.1	8.2

inj, injection; *PD*, prism diopters.

lengths for each patient. Muscle size was quantified by estimating total muscle volume. To estimate muscle volume, cross sections were measured in coronal scans, from the origin at the orbital apex to the point of tangency of muscle with globe. Each cross-sectional area was taken to represent the middle of a cylindrical slab of tissue having a length equal to the slice spacing (3.5 or 4.0 mm) where the axial scan showed a shorter slab at the end of the muscle, the slab volume was reduced accordingly.

We achieved good gaze stability during scans by stabilizing the head and instructing patients to lie with eyes gently closed. There were, however, gaze variations as large as 16° (estimated from axial scans) across scan sessions, some from gaze changes and others as a result of the bupivacaine treatments. Control of gaze, as is done with research subjects[15,16] was not practical with our older patients. Gaze deviation toward the injected muscle, for instance, would cause an anterior segment of that muscle, previously invisible for being wrapped around the globe, to enter the scanned region and contribute to the muscle's calculated volume, tending to inflate the estimate of muscle volume. However, even the largest gaze variation would result in only 3 mm of flat, tendinous, anterior muscle entering or leaving the scan region, and we judged this effect on total muscle volume to be negligible.

Our MRI quantification involved judgments made by readers. Two readers independently made all MRI measurements, and data reported are averages of their measurements. Scan images were coded and processed in random order to minimize systematic errors related to knowledge of patient or time point.

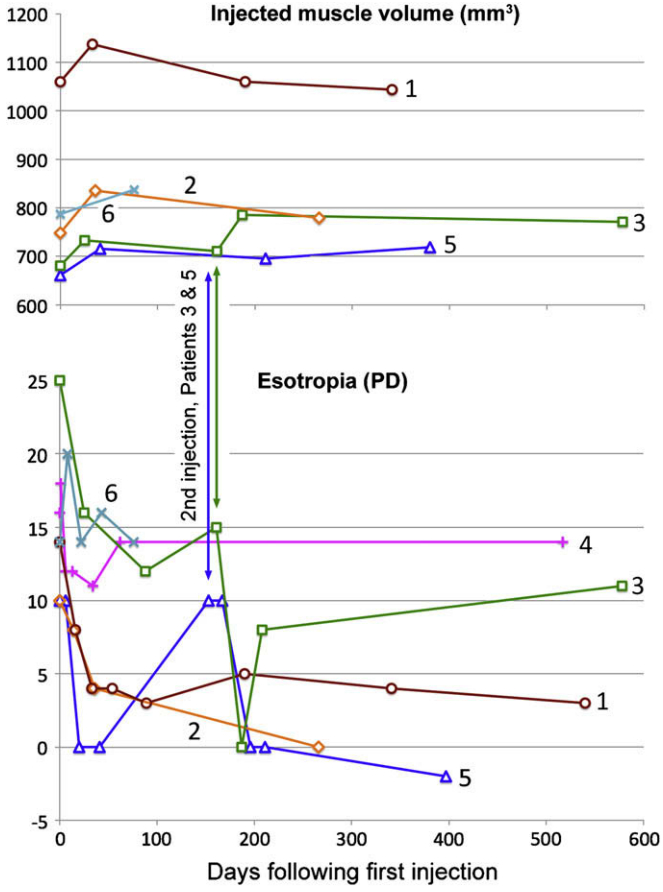

FIG 1. Injected muscle volumes and eye alignment as a function of time after initial injection. Curves are labeled with patient numbers.

Results

Patients

Six patients with moderate-angle esotropia received 1 or 2 bupivacaine injections in a lateral rectus muscle, as described in Table 1.

Muscle Sizes

Injected muscle volumes and primary position misalignments as functions of time are shown in Figure 1. The average volumetric enlargement of the injected muscle was 6.2% (range, –1.5% to 13.3%). The enlargement of the injected muscle reached its maximum around 60 days after injection, declined slightly thereafter, and then was maintained to the end of the observation period, from 76 to 540 days. Patient 1 was an exception, with the lateral rectus muscle returning to the original size by day 200.

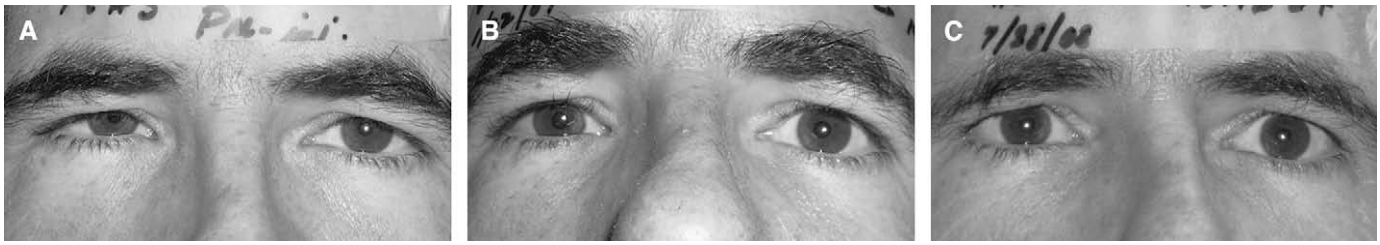

FIG 2. Patient 3: preinjection, 25$^{\Delta}$ esotropia (A); 15$^{\Delta}$ esotropia before second injection, 161 days after first injection (B); and 11$^{\Delta}$ esotropia on day 417 after second injection (C).

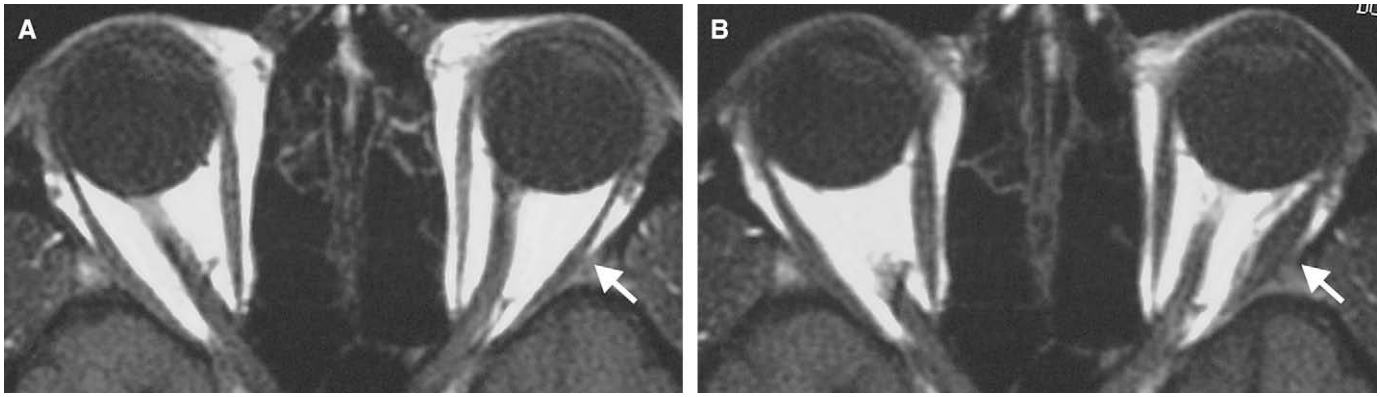

FIG 3. Axial MRI scans of Patient 5 injected with 1.0 mL of bupivacaine into the left lateral rectus: before injection (A) and 20 minutes after injection (B). Note the lack of bupivacaine in the important posterior third of the muscle.

Eye Alignment

The average alignment change for each injection was 6.1$^{\Delta}$. The average final alignment change in the 6 patients was 8.2$^{\Delta}$, with a range of 0$^{\Delta}$ to 14$^{\Delta}$, measured at an average of 343 days after the last injection, with a range of 76 to 540 days (Table 1 and Figures 1 and 2). Patients 4 and 6 received little effect lasting effect. Patient 4 suffered a moderate orbital hemorrhage; we suppose that the hemorrhage displaced the bupivacaine. Patient 6 showed an encouraging muscle enlargement and reduction in esotropia in adduction and abduction to 0 at 42 days, although with the primary position esotropia unchanged. However, his esotropia returned to the original 14$^{\Delta}$ in all gaze directions at 76 days. He declined a second injection. Patients 1, 2, 3, and 5 had useful and lasting improvements in eye alignment, with an average correction of 11.75$^{\Delta}$ at 266 to 540 days after the last injection. The correlation between alignment change and muscle enlargement averaged 0.65, being 0.27, 0.45, 0.92, and 0.95, for Patients 1, 2, 3, and 5, respectively.

Discussion

We believe that a small injection volume does not adequately expose all muscle fibers to the drug, especially in the important posterior third of the muscle. The MRI shown in Figure 3, taken 20 minutes after injection of 1.0 mL, demonstrates this for Patient 5, who received little benefit from this first injection but had a good response to a second, larger injection. Supporting this notion, the incidence of strabismus from orbital anesthetic injection increases with increasing injection volume.[17] We observed no clear effects of the different concentrations of bupivacaine used in these injections.

In most cases, we found a positive correlation between improved alignment and increased volume of the injected muscle. Patient 1, however, showed an enduring 11$^{\Delta}$ improvement in alignment with increase in muscle volume on day 33 that was not maintained (Figure 1). Perhaps, in this patient, new contractile tissue that resulted from bupivacaine injection was better innervated, although not more voluminous, than the tissue it replaced. Perhaps changes in length of the injected muscle or its antagonist at the muscle's ends altered alignment with little change in volume.

The greater initial correction in abduction and adduction than in straight ahead gaze is similar to the pattern seen in many cases of strabismus resulting from orbital anesthetic injections.[10] The modeling program Orbit 1.8™ (Eidactics Visual Biosimulation, San Francisco, CA)[18] shows that only increased muscle contractile force and not increased stiffness can be responsible for increased

range of movement into the field of action of an injected muscle. Increased stiffness alone, related to both contractile and noncontractile elements of an enlarged muscle, tends to decrease range of motion.

Enlargement of the muscle and of the global fibers of the superior rectus muscle of the rabbit injected with bupivacaine is encouraging,[14] as the first report of eye muscle injection of bupivacaine in the rabbit by Park et al[3] showed recovery in the orbital layer only, and no enlargement. A larger and longer study of animal extraocular muscles is clearly needed to clarify differential effects of bupivacaine on contractile and elastic muscle components, and to describe the long-term histological changes occurring in muscle fibers and surrounding tissues. Further clinical studies are needed to define optimal dosages, clarify atypical responses, and determine effects in other strabismus conditions. We continue to follow clinical outcomes of all injected patients to determine stability of alignment and muscle size changes.

Acknowledgments

We thank Vanitha Sankaranarayanan for her help in data analysis and Pacific Vision Foundation for their financial support.

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