Bupivacaine injection of eye muscles to treat strabismus

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Chapter contents

Introduction

Correcting misalignment of deviating eyes is essential to developing and maintaining binocular vision and achieving a normal cosmetic appearance. Surgery on the extraocular muscles (EOM) and optical correction of refractive errors are the classic methods; injection of drugs into the eye muscles to change their action is a third method of altering eye alignment. I will describe the use of bupivacaine (BUP) injection of EOM, the first pharmacologic technique to strengthen the EOMs. It is safe, reliable, and long lasting for small to moderate comitant deviations, about equal in these regards to surgery, with which it will be compared in a pending trial.

Drugs injected into human eye muscles

Alcohol

Behrens, inspired by alignment changes after injection of alcohol into the orbit to reduce eye pain in absolute glaucoma, injected alcohol into the muscles of a few patients with strabismus. The effect was nerve paralysis in one or two and no effect in most. It is reasonable to credit him for this pioneering effort to treat strabismus by direct injection of the extraocular muscles.

Botulinum toxin A

This drug weakens EOM. It was first used for strabismus in 1978; a large experience of its use has been reported since. Chapter 84 addresses this topic.

Collagenase

In 1992, we found that purified bacterial collagenase easily dissolved scleral fibers and intramuscular fibrous tissue in rabbits. We injected the EOM of eight patients in increasing doses, trying to remove fibrous tissue in the EOM in thyroid eye disease and restricting scar formation after orbit fracture. Positive effects were beginning to become evident as the dose was increased, but hemorrhaging from dissolution of collagen in vascular tissues also occurred. It is likely that we terminated these experiments prematurely. Collagenase is now approved by the FDA for use in Dupytren's contracture; injections with good results are usually accompanied by mild bleeding. Application of this drug to restrictive strabismus should be re-visited.

Bupivacaine

BUP enlarges, shortens, and strengthens EOM. We first injected it into EOM as treatment for strabismus in 2006. We have experience with 52 cases of various types, using a range of BUP concentrations and volumes.

Bupivacaine

Mechanism of action

Small lipophilic local anesthetic molecules penetrate cell walls and attach to voltage gated sodium channels of nerves and muscles, blocking propagation of nerve and muscle action potentials. It is reversible and leaves no damage. BUP is especially lipophilic and strongly penetrates the sarcoplasmic reticulum of muscle fibers where it causes myotoxic damage by releasing the stored calcium into the cytosol and blocking calcium re-uptake by the sarcoplasmic reticulum. The high calcium concentration in the cytosol damages the mitochondria of the muscle fiber and activates an enzyme that dissolves the Z-band fibers of the muscle, resulting in separation of the sarcomeres.[1-3] The damaged fibers are not repaired, but are removed over the next few days by macrophages leaving the cell membranes, nerves, and blood vessels intact.[1-8] Within a few hours of exposure to BUP, autocrine growth factor molecules such as insulin growth factors IGF-I and IGF-IEc or mechano growth factor (MGF) are released from the damaged area. These molecules activate the satellite cells that are scattered around each muscle fiber. The satellite cells proliferate and coalesce to form new muscle fibers and myocytes to replace the damaged muscle, a process taking 3 weeks.[1,4,7,9,10,11] In EOM, regeneration builds a muscle that has larger muscle fibers and is increased in size 5–10%, especially in its posterior

third. The regenerated muscle is stiffer than before, probably due to added non-contractile fibrous tissue within the muscle.[9,11,12] These biomechanical alterations change eye alignment.

An EOM treated with BUP appears to regenerate to the length at which it is held during the process of regeneration. Physically restraining the eye to do this is impractical. A small dose of Botox® to the antagonist to weaken it for 3–4 weeks prevents stretching of the BUP injected muscle during the phase of regeneration. This allows the BUP injected muscle to regenerate to a shorter length, doubling the correction effect as compared to use of BUP alone.[13]

Injection volume

The BUP molecule is small and rapidly taken into the blood stream after injection into the highly vascular EOM. Therefore, one cannot deposit a bolus and count on diffusion to carry it through the muscle as occurs with Botox®. A sufficient volume must be injected throughout the muscle to expose the fibers to the BUP. The injection should extend to include the important posterior one-third of the muscle that contributes strongly to contraction and power of the EOM.

The lower volume limit is 2.0 mL, sufficient for the smaller vertical rectus muscles and for small horizontal deviations of 10–15 prism diopters (PD); 3.0 mL is our standard volume. Magnetic resonance imaging (MRI) taken a few minutes after injection shows that the horizontal rectus muscles are fully expanded and are starting to leak after injection of 3.0 mL. The upper useful limit appears to be 4.0 mL. At this volume, BUP breaks out of the EOM and surrounds it, penetrating into the muscle and having a positive effect. Some muscles that were shown by MRI to have been inaccurately injected still achieved a good effect from this outside-in penetration of BUP.

Concentration

Our data show that the effect of BUP on correcting strabismus is dose-related. The usual anesthetic preparations of 0.50% and 0.75% BUP are adequate for strabismus of 10–15 PD. We use 1.50% to 2.50% BUP for larger deviations, reserving 3.00% for the largest angles. Compounding pharmacies can provide 3.00% BUP, which then can be diluted with saline to effect lower concentrations.

Toxicity and safety

Orbital tissues

BUP has been injected into innumerable orbits for cataract anesthesia. Except for rare physical damage from the needle and occasional myotoxic damage when inadvertently injected into EOM, the drug appears harmless. Bathing the anterior EOM and surrounding tissues with 2–3 mL of 0.75% BUP for postoperative pain relief after strabismus surgery is innocuous and without myotoxic effect. In our patients, injection of BUP into the orbit in concentrations up to 3.00% does not damage any tissue except muscle. Even when complete block of the optic nerve and motor nerves has occurred it has reversed fully.

Increased fibrosis around muscles treated with BUP injection might be a mechanism of action. However, we did not encounter this in the muscles of two patients we operated after injection, nor is it remarked in the many reports of surgery for myotoxic strabismus after cataract surgery. Nevertheless, the muscle damage caused by BUP does cause inflammation; this must be considered an open issue.

Muscles

BUP damage to muscle causes inflammation with removal of the necrotic fibers and myocytes by macrophages. With small BUP doses, this is usually subclinical inflammation. However, necrosis of most of the EOM from a large dose such as 3.0 mL of 3.00% BUP creates redness, swelling, and discomfort for 2–3 days before the EOM tissue is absorbed. Preventive use of oral prednisone, starting with 50 mg on the day of BUP injection for an average adult and declining by 10 mg steps for three subsequent daily doses, will markedly reduce such inflammation.

Systemic toxicity

BUP in healthy patients is considered safe in intravenouis doses below 1.5 mg/kg body weight. We have used up to 2.0 mg/kg to inject multiple EOMs without adverse reaction. Large vessels exist in the posterior part of the EOM and orbit where the BUP is injected; needle aspiration should be routine before orbital BUP injections.

Injection technique (Video 87.1)

We use topical proparacaine 0.5%, then a vasoconstrictor such as brimonodine, then proparacaine each minute for 4 minutes. For previously unoperated muscles, insert the electrode needle 12 mm posterior to the limbus. If there was earlier recession surgery, insert the needle further posterior. The posterior extent of the EOM is at least 10–15 mm further back than usual Botox® injection sites. With electromyography (EMG) guidance showing that the needle is in the EOM, the necessary posterior location of the injection can be done with assurance. Aspirate to ensure the needle is not intravascular. Inject 0.25 mL of BUP and wait for the EMG sound to become quiet as the muscle and nerves are anesthetized. Then continue to inject, slowly so as not to blow up the muscle suddenly. Plan to put about two-thirds into the posterior third of the EOM; the remainder is injected into the middle third of the EOM. If resistance to injection develops, retract forward a few millimeters until injection can proceed easily.

Results of BUP injection

In 23 patients with comitant strabismus, the average correction of the deviation was 70% at 6 months after injection. Except for technical errors of injection and some early trials with doses too small, all BUP injections have had an effect; BUP injection into EOM is reliable in changing alignment.

In an earlier report, six patients with comitant esotropia treated with BUP alone were corrected an average 8.2 PD after an average of 343 days.[14] Revisiting these patients at an average postinjection interval of 736 days, we find the average deviation to be 7.4 PD.

In an earlier report, seven patients with comitant strabismus injected with both BUP and Botox® were corrected an average of 19.7 PD at 193 days after injection.[13] Revisiting these patients at an average postinjection interval of 602 days, we find the average deviation to be 19.3 PD.

Wutthiphan and Srisuwanporn injected one horizontal rectus muscle in 20 patients with horizontal strabismus, using

4.50 mL of 0.50% BUP. Thirteen of 15 comitant patients were improved. The average improvement was 8–9 PD, and was the same at 1, 3, 6, and 12 months after injection.[15] They found improvement in 13 of 15 comitant patients, but only two of five incomitant cases. This is similar to our experience (see below); paralyzed, restricted, or damaged muscles do not respond as well to BUP injection as do the muscles in comitant strabismus.

Clinical course after injection

BUP alone gives a day of anesthesia of the injected EOM (and often of other tissues) followed by a week of mild weakness from the myotoxicity, then 2–3 weeks of progressive improvement. The outcome of the injection procedure will be evident at 1 month.

BUP and Botox® given together weaken agonist and antagonist about equally, reducing ductions in both directions. This typically leaves the treated eye with little alignment change until regeneration gives improved muscle function at 3 to 4 weeks after injection (Fig. 87.1).

Increased muscle action

In mild incomitant deviations without muscle paralysis, it is often desirable to increase action of an EOM. BUP makes this possible. The ambylopic 32 mm diameter left eye in Figure 87.2 (upper panel) could be only partially corrected to 20 PD left exotropia by multiple Botox® injections to the left lateral rectus (LLR). BUP injection of the left medial rectus (LMR) both aligned and retracted the left eye with a result that was stable for over 2 years (Fig. 87.2, lower panel).

Josephson and Mathias treated patients with symptomatic convergence insufficiency unresponsive to orthoptic training or prismatic glasses by injection of one or both medial rectus muscles with BUP. They corrected the average deviation of 11 patients from 12.6 PD to 5.3 PD, measured at 1 year after injection. Nine patients were without symptoms, one patient required prism glasses, and one patient required surgical correction.[16]

Special cases

Muscle atrophy

BUP did not work in five patients with atrophic lateral rectus muscles after sixth nerve paralysis. Some of these EOMs were injected several times, attempting to "grow" a bigger and stronger muscle. All patients remained without substantial change. We suggest that the absence of satellite cells around these atrophic muscles is the reason for this lack of response. Direct injection of stimulating molecules such as MGF may yet be useful in these muscles, as may be transplantation of muscle cells with BUP or transplantation of stem cells. The great need

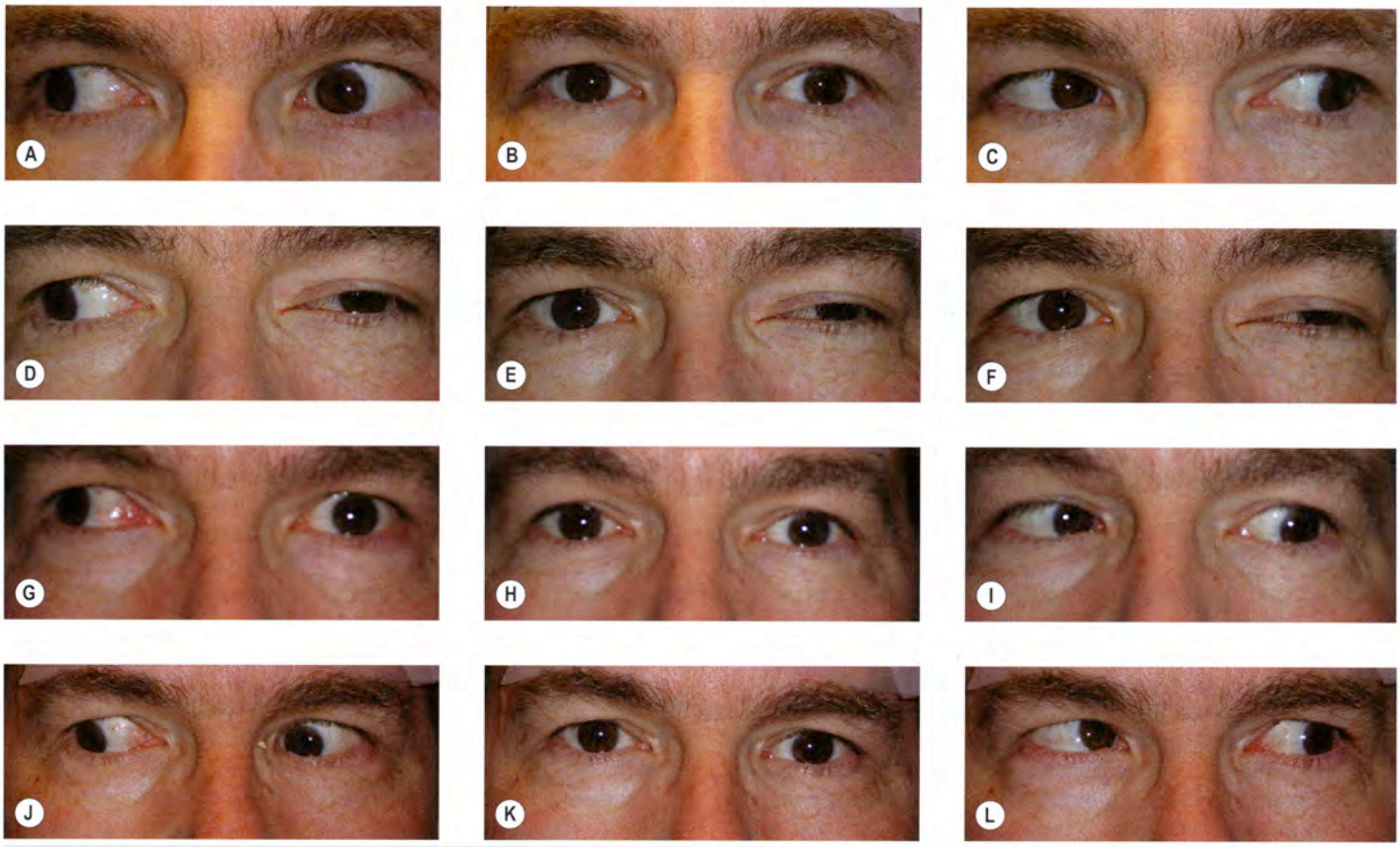

Fig. 87.1 Sequence of events after injection of BUP to LMR and Botox® to LLR. (Top row) Pre-injection, 16 PD exotropia following two operations for esotropia and three Botox® injections of the LLR for exotropia. (Second row) 30 minutes after injections with paralysis of the LMR. (Third row) 13 days after injections, 16 PD exotropia, with weakness of both the LMR and LLR. (Bottom row) 355 days after injection, 6 PD exotropic. (Modified from Scott AB, et al. Treating strabismus by injecting the agonist muscle with bupivacaine and the antagonist with botulinum toxin. Trans Am Ophthalmol Soc 2009; 107: 104–109. Republished with permission of the American Ophthalmological Society.)

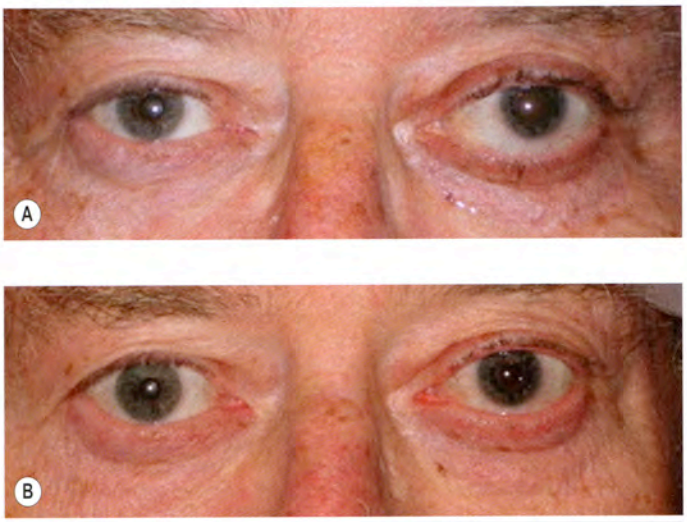

Fig. 87.2 (A) 20 PD exotropia of amblyopia 32.0 mm long myopic left eye after three injections of left lateral rectus with Botox®. (B) Left eye straight and also retracted 2.0 mm at 722 days after BUP injection of LMR and Botox® injection of LLR.

for a technique to strengthen weak EOM will attract several solutions beyond BUP.

Denervation without atrophy

BUP worked well in one partially paralyzed lateral rectus muscle without atrophy and in the muscles in one case of cranial third nerve paresis with anomalous regeneration. It appears that the extent of muscle atrophy, not the extent of innervation, determines BUP effectiveness.

Injection of BUP and Botox® into the same muscle

In three patients we injected both BUP and Botox® into the same muscle, testing the idea that the treated muscle would be stretched by the antagonist during regeneration and thereby result in a longer muscle. This did not elongate the muscle; two of the three cases experienced slight worsening of the strabismus as the muscle shortened.

Larger deviations

The limit of effect of BUP and Botox® injected together seems to be about 30 PD. However, repeated injections are additive. Figures 87.3 and 87.4 show the change in alignment and in EOM sizes in one such case.

High myopia with acquired esotropia from muscle displacement

One case has a correction of 30 PD of esotropia from combined BUP and Botox® and remains stable at 1 year. A second case has reduction of 40 ET to 18 ET. We suggest that the enlarged and stiffened lateral rectus muscle remains effective as an abductor and does not slide inferiorly as it did in its stretched pre-injection condition. Both cases required two injection treatments to effect these changes.

Ptosis correction

Four of six adults with acquired ptosis and apraxia of eyelid opening associated with blepharospasm have shown 1–3 mm of upper eyelid elevation after treatment of the levator

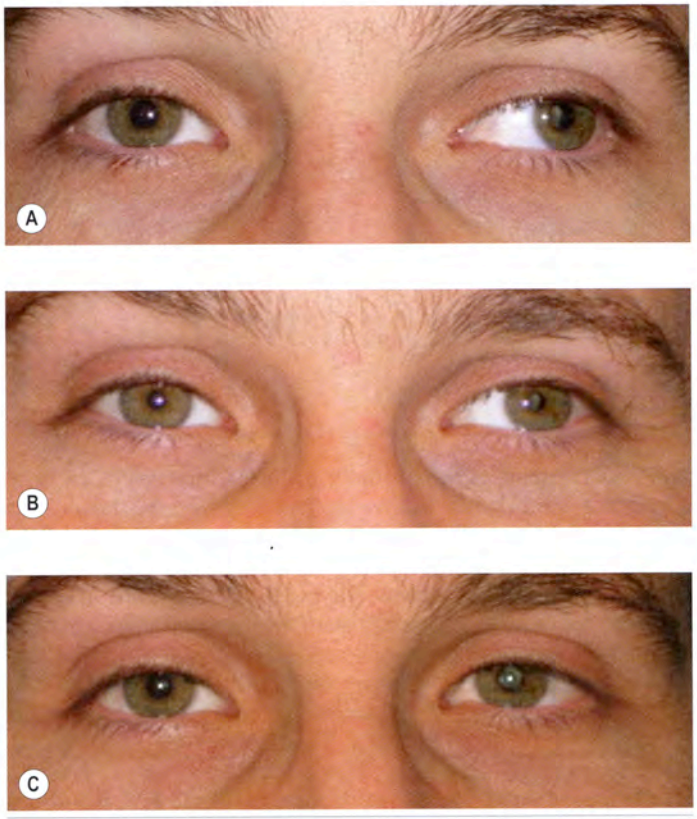

Fig. 87.3 (A) Congenital cataract with amblyopia, 50 PD exotropia. (B) 55 days after injection of left medial rectus with BUP, and left lateral rectus with Botox®. (C) Left eye re-injected at 55 days after first injection; this image 2.5 years after second injection.

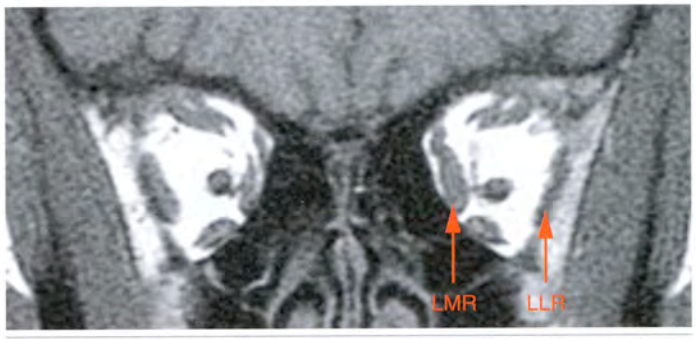

Fig. 87.4 MRI of patient from Figure 87.3 at 224 days after second injection of left medial rectus (LMR) with BUP and left lateral rectus (LLR) with Botox®. Notice that the LMR is larger, and LLR is smaller than the corresponding muscles in the right eye.

palpebrae with 3.0 mL of 3.0% BUP. These are presumed to be normal muscles that have been stretched. The utility of BUP injection in patients with ptosis due to abnormally developed levator muscles remains to be defined.

Children with strabismus

We have no data on the effect of BUP in children. Patients aged 18 to 89 have shown little variation in response to BUP, and our experience in the laboratory with animals of various ages shows no discernible effect of age on the action of BUP. We suppose that BUP action in children will be about the same as that in adults (Table 87.1).

Table 87.1 – Usage of BUP in adults

Condition	Treatment
Comitant strabismus of 6–12 PD	2.0–3.0 mL of 1.5% BUP
Comitant strabismus of 12–30 PD	3.0 mL of 1.5% to 2.5% BUP and 1.0 to 2.0 units Botox®
Comitant strabismus of >30 PD	3.0 mL of 3.0% to 2.5% BUP and 2.0 to 5.0 units Botox®
Non-paralytic ptosis	3.0 mL of 3.0% BUP injected through the upper lid

Summary

BUP injection of EOM, initially an accidental event causing unwanted strabismus following retrobulbar anesthesia, has emerged as a controllable and useful treatment modality. BUP alone, or together with Botox® is safe and effective in the treatment of moderate deviations of up to 30 PD in adults. Its place in the treatment of other forms of strabismus remains to be defined.

Acknowledgments

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