# Injection Treatment of Strabismus

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## Strabismus Treatment

*Strabismus* is misalignment of the eyes caused by imbalances in the actions of the muscles that rotate them. Causes can be congenital or traumatic, *central* (in the brain) or *peripheral* (in the *orbit,* the eye, eye muscles, and surrounding tissues), but regardless of etiology, treatment is usually surgical, performed under general anesthesia at the *insertional* ends of muscles (where they attach to the globe). *Resection* surgery removes tissue in order to stretch a muscle, increasing its elastic force; *recession* moves an insertion so as to reduce stretch, and so reduce elastic force; *transposition* moves an insertion "sideways", sacrificing one direction of muscle action for another; *posterior fixation* relocates a muscle's effective insertion to a mechanically disadvantageous position, reducing its effectiveness in eccentric gaze. All restore balance by means of compensatory impairment.

Pharmacologic injection treatment, in contrast, offers the possibility of directly altering contractile muscle strength and elastic stiffness, as well as changing muscle length, without removing tissue or otherwise compromising orbital mechanics.

Most strabismus patients are children, in whom early correction can facilitate normal visual and social development. But there are reasons to think that such general anesthesia as is required for conventional surgery may damage the developing brain (Mcgowan & Davis 2008; Flick et al 2011; Mccann 2011; Ing et al 2012; Stratmann et al 2014) and it has been recommended that anesthetic procedures in young children be kept brief (Good 2014). Injection methods for children compatible with minimal anesthesia are already available for some pharmacologic agents, and are being developed for others (Debert et al 2015 in press).

Spherical lenses and *miotic* eye drops can provide relief in some types of horizontal strabismic misalignment by biasing the neural link between *convergence* (orienting the lines of sight for near objects) and *accommodation* (focusing), and prism lenses can relieve *diplopia* (double vision) by refracting the visual axis, but these treatments don't address underlying muscular imbalances.

## Injection Treatment

Pharmacologic injection treatments can be given to cooperative adults under local anesthesia in an outpatient setting, and for some agents, under light general anesthesia (Mcneer et al 1999; De Alba Campomanes et al 2010). In the former case, it is possible to bring the injection needle to an optimal location in the desired muscle using EMG guidance (Magoon et al 1982). As the alert patient looks in diagnostic directions, the needle is advanced until the *electromyogram* (the electrical signal from an activated skeletal muscle) indicates it is optimally positioned, whereupon the injection is completed. Some agents (eg, botulinum toxin) can be injected at the insertional end of a muscle under visual guidance, using special forceps that make the muscle more accessible (Mendonca et al 2005), and allowed to diffuse posteriorly, whereas others (eg, bupivacaine) must be distributed throughout the body of the muscle (Park et al 2004), which requires non-visual guidance. EMG guidance generally provides more effective injections, but is only suitable for alert, cooperative adults.

Children, and others unable to provide the requisite cooperation during injection, would need to be briefly anesthetized, making it impossible to record the movement-related EMG. For cases where visual guidance is insufficient, methods are being developed for targeting injections using electrical stimulation, which early results show to be effective in anesthetized patients (Debert et al 2015 in press).

Because injection treatment does not result in the scaring that is often a troublesome consequence of conventional strabismus surgery, if therapeutic goals are not achieved with one injection, additional injections or surgical treatments can readily be given. Conversely, injection treatment may be particularly useful where post-surgical scarring has made re-operation difficult.

## Muscle Weakening

Replacement of strabismus surgery with less invasive procedures began in Alan B Scott's San Francisco lab with his development of botulinum A toxin injection treatment (Scott et al 1973; Scott 1980).

Eye muscle balance can sometimes be restored by weakening a muscle that pulls too strongly, or pulls against another that has been weakened by disease or trauma. Botulinum toxin prevents neurotransmitter release from neuromuscular junctions, and so at least partially paralyzes injected muscles. Paralysis is temporary, and it might seem that injections would always need to be repeated, except that muscles adapt to the lengths at which they are chronically held, so that a paralyzed muscle tends to get stretched-out by its antagonist (where there is one) and grows longer by addition of serial *sarcomeres* (the contractile units of skeletal muscles), while the antagonist tends to grow shorter by deletion of sarcomeres (Scott 1994), thereby maintaining re-alignment when the toxin-caused paralysis has resolved. If there is good binocular vision, once muscular imbalance is sufficiently reduced, the brain mechanism of *motor fusion* (which orients the eyes to a target visible to both) can perfect and stabilize eye alignment.

Botulinum A toxin (introduced as *Oculinum™*, now called *Botox®*), is the principal drug used to temporarily paralyze extraocular muscles, and is widely accepted as an alternative to surgery for many types of strabismus (Crouch 2006; Rowe & Noonan 2012). *Crotoxin*, a snake neurotoxin, is being developed in Belo Horizonte, Brazil as a potential alternative (Ribeiro Gde et al 2012).

## Mechanism of Action

The force exerted by a muscle is the sum of its *contractile force* ("active" force, controlled by neural innervation) and its *elastic force* ("passive" force, determined stretching). Both are affected by *muscle length*, which determines the degree of stretch in a given eye position. Botulinum toxin paralysis reduces total muscle force by reducing the contractile component.

Botulinum A toxin is a neurotoxin present in the cytoplasm of the anaerobic bacterium *Clostridium botulinum*. It binds presynaptically with high affinity to sites on cholinergic nerve terminals, preventing release of acetylcholine, thereby blocking neuromuscular transmission, and causing flaccid muscle paralysis (Montecucco et al 1996; Tighe & Schiavo 2013). Crotoxin appears to act similarly.

Botulinum toxin inactivates proteins necessary for neurotransmitter release without damaging the neuromuscular junction itself. The body copes with such *chemodenervation* by sprouting axonal collaterals to form new neuromuscular junctions, and eventually by breaking down the toxin, leading to recovery of muscle function (Angaut-Petit et al 1990; De Paiva et al 1999).

To weaken an eye muscle, 1 to 12 units (a few nanograms) of toxin are injected directly into it. The treated muscle weakens over 48-72 hours and remains *paretic* (partially paralyzed) for 2-4 months, over which time muscle length increases (Scott 1994). If there is good binocular vision, the brain mechanism of *motor fusion*, which aligns the eyes on a target visible to both, can stabilize the corrected alignment.

## Clinical Indications

Botulinum toxin injection is commonly used for small and moderate degrees of infantile *esotropia* ("crossed eyes"), acquired adult strabismus, and where strabismus is a consequence of retinal detachment surgery, that is, in cases where there is good potential for motor fusion.

*Sixth nerve palsy,* paralysis of the *lateral rectus*, the muscle that rotates the eye outwards, is most frequently caused by a local ischemic event, from which there is frequently substantial recovery. But during the acute stage of paresis, the lateral rectus is stretched and grows longer, and its antagonist medial rectus shortens (Scott 1994). Sixth nerve palsy is treated by injecting the medial rectus muscle, thereby allowing the lateral rectus, paretic though it be, to stretch and lengthen the medial, while it itself shortens, so that, when the sixth nerve paresis subsides, alignment is improved (Mcneer et al 1999; Kowal et al 2007). The toxin is similarly useful in other nerve palsies affecting eye muscles.

Residual misalignments that remain following traditional strabismus surgery can be corrected with toxin injection (Mcneer et al 1999; Kowal et al 2007).

Toxin injections are also used for temporary relief during the acute phase of *thyroid ophthalmopathy* (an autoimmune inflammatory disorder), when misalignments are too unstable to treat surgically.

Botulinum toxin has been used intraoperatively to augment a surgical effect.

In complex strabismus cases, toxin can be injected diagnostically as an aid to planning surgical treatment.

### Complications

Subconjunctival hemorrhage, *ptosis* (drooping eyelid) and vertical strabismus are the most common complications, usually resolving in several weeks (Crouch 2006; Rowe & Noonan 2012). Ptosis and vertical strabismus are caused by toxin spreading to adjacent muscles, and their risk decreases with lower doses and more accurate injection techniques.

Some *overcorrections*, such as *exotropia* (eyes deviated outward) following treatment for infantile *esotropia* ("crossed eyes"), may lead to excellent long-term alignment, and are not complications.

Severe complications, such as globe perforation and retrobulbar hemorrhage are rare.

No systemic side effects have been reported in patients treated for strabismus, nor has immunity to botulinum toxin developed, even after multiple injections.

## Muscle Strengthening

### Bupivacaine

Bupivacaine injection is currently the only pharmacologic treatment clinically shown to strengthen and shorten extraocular muscles. Myogenic growth factors (IGF and FGF) have been investigated in animals (Anderson et al 2006; Mcloon 2006).

Long used as an anesthetic in cataract surgery, bupivacaine was found to sometimes cause strabismus, presumably because it had been inadvertently injected into a muscle. Initially attributed to simple myotoxic damage (Rainin & Carlson 1985), careful observation of the clinical time course showed more complex sequelae, including increased contractility and elevated stiffness (Goldchmit & Scott 1994). It was later clarified that bupivacaine injection induces modest hypertrophy, which could be harnessed to produce muscle shortening and alignment corrections (Miller et al 2013). Bupivacaine injection is currently an office procedure performed under topical anesthesia in cooperative adults, and has been used as an alternative to strabismus surgery to treat moderate-sized, non-paralytic, non-restrictive strabismus since 2006 (Scott et al 2007; Miller et al 2013). Stability of alignment correction has been documented for up to 5 years (Debert et al 2015 in press).

### Mechanism

Bupivacaine damages or destroys *myofibrils* (the specialized elements in skeletal muscle cells responsible for contractile and elastic forces), while preserving *satellite cells* (local stem cells supporting repair and regeneration), *basal lamina* (an extracellular framework), capillaries, and peripheral nerves (Nonaka et al 1983). It induces calcium release from the *sarcoplasmic reticulum* (an intracellular structure), inhibits reuptake, and sensitizes the contractile apparatus to calcium (Zink et al 2002), so that within a few minutes of injection myofibrils hypercontract and damage to plasma membranes is evident (Bradley 1979). Within a few hours, *calcium-activated neutral protease* (CANP) localized in Z-lines (Ishiura et al 1980) cleaves the sarcomeres, which are then digested by other proteases and lysosomal enzymes (Imahori 1982). Within a few weeks, satellite cells proliferate, and fuse into new muscle fibers (Hall-Craggs 1974; Bradley 1979), which are generally larger and stronger.

Following transient increases in muscle size (and so, presumably, in both contractile and elastic forces), BPX treatment results in stable changes in muscle lengths (Miller et al 2013).

### Adjuvants

The length at which the muscle treated with bupivacaine regenerates is determined by the length at which it is held during regeneration. Injection of small dose of botulinum toxin in the antagonist muscle weakens it for a few weeks, preventing stretching of the bupivacaine-injected muscle, allowing it to regenerate shorter than otherwise, thereby providing about twice the alignment correction of bupivacaine alone. The effectiveness of a bupivacaine injection may be increased by combining it with the vasoconstrictor epinephrine, which lengthens exposure time (Miller et al 2013).

## Pharmacologic Injection Treatment vs Surgery

With surgery, results are seen in a few days. After bupivacaine injection the muscle is inactivated by the drug's anesthetic effect for a day, and weakened by myofiber destruction for a week or so, after which regeneration and hypertrophy over 2-3 weeks gradually achieves the corrected alignment (Miller et al 2013). If bupivacaine injection is combined with a small dose of botulinum toxin in the antagonist muscle, eye deviation during regeneration is minimized.

Strabismus surgery generally sacrifices one mechanical effect to gain another, and always causes scarring, both of which may make any subsequent procedures more difficult. Bupivacaine injection treatment, in contrast, directly increases muscle strength and reduces length.

Strabismus surgery requires an operating room, anesthetist, and other personnel, whereas bupivacaine injection in cooperative adults is an office procedure taking only a few minutes.

Bupivacaine injection is not effective in paralyzed or atrophic muscles, or where there are restrictions to movement elsewhere in the orbit (eg, fibrotic muscles). Very small misalignments might be better treated surgically where there is the risk that overcorrection would cause diplopia.

## Bibliography


Anderson BC, Christiansen SP, Grandt S, Grange RW, Mcloon LK (2006). Increased extraocular muscle strength with direct injection of insulin-like growth factor-i. *Investigative Ophthalmology & Visual Science*, vol 47, isu 6, pgs 2461-2467.

Angaut-Petit D, Molgo J, Comella JX, Faille L, Tabti N (1990). Terminal sprouting in mouse neuromuscular junctions poisoned with botulinum type a toxin: Morphological and electrophysiological features. *Neuroscience*, vol 37, isu 3, pgs 799-808.

Bradley WG (1979). Muscle fiber splitting. In: Mauro A ed. Muscle regeneration. New York, Raven Press. Pp. 215-232.

Crouch ER (2006). Use of botulinum toxin in strabismus. *Curr Opin Ophthalmol*, vol 17, isu 5, pgs 435-440.

De Alba Campomanes AG, Binenbaum G, Campomanes Eguiarte G (2010). Comparison of botulinum toxin with surgery as primary treatment for infantile esotropia. *J AAPOS*, vol 14, isu 2, pgs 111-116.

De Paiva A, Meunier FA, Molgo J, Aoki KR, Dolly JO (1999). Functional repair of motor endplates after botulinum neurotoxin type a poisoning: Biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proc Natl Acad Sci U S A*, vol 96, isu 6, pgs 3200-3205.

Debert I, Miller JM, Danh KK, Scott AB (2015). Pharmacologic treatment of comitant strabismus. J AAPOS.

Flick RP, Katusic SK, Colligan RC, Wilder RT, Voigt RG, Olson MD, Sprung J, Weaver AL, Schroeder DR, Warner DO (2011). Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. *Pediatrics*, vol 128, isu 5, pgs e1053-1061.

Goldchmit M, Scott AB (1994). Avaliacao da motilidade extrinseca ocular de pacientes facectomizados sob anestesia retrobulbar. *Arq. Bras. Oftalmol.*, vol 57, isu 2, pgs 114-116.

Good WV (2014). Is anesthesia safe for young children? *J AAPOS*, vol 18, isu 6, pgs 519-520.

Hall-Craggs EC (1974). Rapid degeneration and regeneration of a whole skeletal muscle following treatment with bupivacaine (marcaine). *Experimental Neurology*, vol 43, isu, pgs 349-358.

Imahori K (1982). Calcium-dependent neutral protease: Its characterization and regulation. In: Cheung WY ed. Calcium and cell function. New York, Academic Press. Pp. 473-485.

Ing C, Dimaggio C, Whitehouse A, Hegarty MK, Brady J, Von Ungern-Sternberg BS, Davidson A, Wood AJ, Li G, Sun LS (2012). Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics*, vol 130, isu 3, pgs e476-485.

Ishiura S, Sugita H, Nonaka I, Imahori K (1980). Calcium-activated neutral protease: Its localization in the myofibril, especially at the z-band. *Journal of Biochemistry*, vol 87, isu 1, pgs 343-346.

Kowal L, Wong E, Yahalom C (2007). Botulinum toxin in the treatment of strabismus. A review of its use and effects. *Disabil Rehabil*, vol 29, isu 23, pgs 1823-1831.

Magoon E, Cruciger M, Scott AB, Jampolsky A (1982). Diagnostic injection of xylocaine into extraocular muscles. *Ophthalmology*, vol 89, isu 5, pgs 489-491.

Mccann ME (2011). Anesthetic neurotoxicity in babies. *J AAPOS*, vol 15, isu 6, pgs 515-517.

Mcgowan FX, Jr., Davis PJ (2008). Anesthetic-related neurotoxicity in the developing infant: Of mice, rats, monkeys and, possibly, humans. *Anesth Analg*, vol 106, isu 6, pgs 1599-1602.

Mcloon LK, Anderson, B., & Christiansen, S. P. (2006). Effect of basic fibroblast growth factor (fgf2) on force generation in rabbit extraocular muscle. Investigative Ophthalmology & Visual Science. pgs 2930-2930.

Mcneer KW, Magoon EH, Scott AB (1999). Chemodenervation therapy: Techniques and indications. In: Rosenbaum A, Santiago AP ed. Clinical strabismus management. Philadelphia, W. B. Saunders. Pp. 423-432.

Mendonca TF, Cronemberger MF, Lopes MC, Nakanami CR, Bicas HE (2005). Electromyograph assistance and mendonca's forceps -- a comparison between two methods of botulinum toxin a injection into the extraocular muscle. *Arq Bras Oftalmol*, vol 68, isu 2, pgs 245-249.

Miller JM, Scott AB, Danh KK, Strasser D, Sane M (2013). Bupivacaine injection remodels extraocular muscles & corrects comitant strabismus. *Ophthalmology*, vol 120, isu 12, pgs.

Montecucco C, Schiavo G, Tugnoli V, De Grandis D (1996). Botulinum neurotoxins: Mechanism of action and therapeutic applications. *Mol Med Today*, vol 2, isu 10, pgs 418-424.

Nonaka I, Takagi A, Ishiura S, Nakase H, Sugita H (1983). Pathophysiology of muscle fiber necrosis induced by bupivacaine hydrochloride (marcaine). *Acta Neuropathol*, vol 60, isu 3-4, pgs 167-174.

Park CM, Park SE, Oh SY (2004). Acute effects of bupivacine and ricin mab 35 on extraocular muscle in the rabbit. *Curr Eye Res*, vol 29, isu 4-5, pgs 293-301.

Rainin EA, Carlson BM (1985). Postoperative diplopia and ptosis. A clinical hypothesis based on the myotoxicity of local anesthetics. *Arch Ophthalmol*, vol 103, isu 9, pgs 1337-1339.

Ribeiro Gde B, Almeida HC, Velarde DT (2012). Crotoxin in humans: Analysis of the effects on extraocular and facial muscles. *Arq Bras Oftalmol*, vol 75, isu 6, pgs 385-389.

Rowe FJ, Noonan CP (2012). Botulinum toxin for the treatment of strabismus. *Cochrane Database Syst Rev*, vol 2, isu, pgs CD006499.

Scott AB (1980). Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology*, vol 87, isu 10, pgs 1044-1049.

Scott AB (1994). Change of eye muscle sarcomeres according to eye position. *J Pediatr Ophthalmol Strabismus*, vol 31, isu 2, pgs 85-88.

Scott AB, Rosenbaum A, Collins CC (1973). Pharmacologic weakening of extraocular muscles. *Invest Ophthalmol*, vol 12, isu 12, pgs 924-927.

Scott AB, Alexander DE, Miller JM (2007). Bupivacaine injection of eye muscles to treat strabismus. *Br J Ophthalmol*, vol 91, isu 2, pgs 146-148.

Stratmann G, Lee J, Sall JW, Lee BH, Alvi RS, Shih J, Rowe AM, Ramage TM, Chang FL, Alexander TG and others (2014). Effect of general anesthesia in infancy on long-term recognition memory in humans and rats. *Neuropsychopharmacology*, vol 39, isu 10, pgs 2275-2287.

Tighe AP, Schiavo G (2013). Botulinum neurotoxins: Mechanism of action. *Toxicon*, vol 67, isu, pgs 87-93.

Zink W, Graf BM, Sinner B, Martin E, Fink RHA, Kunst G (2002). Differential effects of bupivacaine on intracellular ca2+ regulation: Potential mechanisms of its myotoxicity. *Anesthesiology*, vol 97, isu 3, pgs 710-716.