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 by 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


