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Botulinum Toxin in the treatment of strabismus. A review of its use and effects

LIONEL KOWAL[1,2], ELAINE WONG[1,2] & CLAUDIA YAHALOM[3]

[1]*Ocular Motility Unit, Royal Victorian Eye and Ear Hospital, Melbourne,* [2]*Centre for Eye Research, Australia, and* [3]*Ophthalmology, Hadassah Hospital, Jerusalem, Israel*

Abstract

Botulinum Toxin as a medical therapy was introduced by Dr Alan Scott more than 20 years ago. The first clinical applications of Botulinum Toxin type A (BT-A) were for the treatment of strabismus and for periocular spasms. Botulinum Toxin type A is often effective in small to moderate angle convergent strabismus (esotropia) of any cause, and may be an alternative to surgery in these cases. Botulinum Toxin type A may have a role in acute or chronic fourth and sixth nerve palsy, childhood strabismus and thyroid eye disease. The use of BT-A for strabismus varies enormously in different cities and countries for no apparent reason. Botulinum Toxin type A may be particularly useful in situations where strabismus surgery is undesirable. This may be in elderly patients unfit for general anaesthesia, when the clinical condition is evolving or unstable, or if surgery has not been successful. Botulinum Toxin type A can give temporary symptomatic relief in many instances of bothersome diplopia irrespective of the cause. Ptosis and acquired vertical deviations are the commonest complications encountered. Vision-threatening complications are rare. Repeated use of BT-A is safe.

Keywords: *Strabismus, Botulinum Toxin type A, ocular Motility disorders*

Introduction

The use of Botulinum Toxin type A (BT-A) for strabismus was first described and developed by the American ophthalmologist Dr Alan Scott in the early 1980s [1,2]. He personally trained hundreds of ophthalmologist collaborators in its use (including the author LK) and carefully collated data from his own and their work over some years to demonstrate the effects of BT-A. Botulinum Toxin type A was subsequently approved by the Food and Drug Authority [USA] for both adult strabismus and blepharospasm in 1989. Since then, BT-A has been used by a small number of ophthalmologists (usually strabismus specialists) as an easier and less invasive alternative to strabismus surgery in selected cases. Regrettably, prospective randomized controlled trials on the use of BT-A in different strabismus entities comparing the effect of BT-A to that of surgery have yet to be performed.

There are a small number of centres where BT-A is used frequently in the treatment of strabismus. The Toxin Clinic at the Moorfields Eye Hospital in London had given 18,000 BT-A injections for strabismus by the end of 2005. The Gomez family of ophthalmologists in Madrid have given 7,000 BT-A injections for strabismus until 2005. These two groups, and that of the developer Alan Scott in San Francisco, stand out as the most experienced centres internationally in the use of BT-A in strabismus.

In Australia, there are about 10 ophthalmologists who have been trained in the use of BT-A for strabismus, usually in London or San Francisco. Statistics on the use of BT-A in strabismus in Australia are available from the Medicare Australia website. The data does not include patients who are treated in public hospitals or whose treatment is not billed through Medicare Australia, e.g., those paid by Workcover companies. Only 70 – 80 BT-A treatments for strabismus a year are recorded on the

Correspondence: Dr Lionel Kowal, The Private Eye Clinic, Level 3, 182 Victoria Parade, East Melbourne VIC 3002, Australia.
E-mail: strabism@netspace.net.au

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Medicare Australia website (www.medicareaustralia.gov.au) throughout the country.

Botulinum Toxin type A is usually injected directly into the selected extraocular muscle in the ophthalmologists' office under topical anaesthesia, usually with electromyographic (EMG) guidance. Patient cooperation is required. The 'chair time' is typically 10–15 min, and time lost from work is typically 2–3 h. The effect of BT-A will start to be seen within 2–4 days of the injection, it then causes an overcorrection for some weeks ('the effect'), which then wears off after 6–8 weeks leaving a permanent realignment ('the after-effect') in many cases.

Botulinum Toxin type A may be particularly useful in situations where strabismus surgery is undesirable. This may be in elderly patients unfit for general anaesthesia, when the clinical condition is evolving or unstable, or if surgery has not been successful. Botulinum Toxin type A can give temporary symptomatic relief in many instances of bothersome diplopia irrespective of the cause.

Strabismus

Strabismus arises when there is imbalance in extraocular muscle function resulting in misalignment of the eye or eyes. The foveas will not both be directed at the same object and (if both eyes see well) there will be diplopia and confusion.

The muscular control of eye movements can be likened to the reins of a horse – when one muscle contracts (agonist), the other relaxes (antagonist). Both reins do not contract at the same time unless innervation is anomalous. There are 3 different sets of reins for each eye, for horizontal, vertical and torsional movements. The actions of the 3 sets of muscle in one eye are intricately linked to the actions of the 3 sets of the other eye. Each rein forms part of one of 3 pairs of agonist and antagonist extraocular muscles, the primary actions of which are:

(1) Horizontal movement:
    (a) Medial rectus (MR) – adduction (moving the eye towards the nose)
    (b) Lateral rectus (LR) – abduction (towards the ear)
(2) Vertical movement:
    (a) Superior rectus (SR) – elevation
    (b) Inferior rectus (IR) – depression
(3) Torsional movement:
    (a) Superior oblique (SO) – intorsion (clockwise rotation of the right eye, anti- clockwise of the left eye)
    (b) Inferior oblique (IO) – extorsion.

When there is an imbalance of one or more of these muscles sets, strabismus results. The actions of the rein sets are not 'pure' and there is some overlap. The primarily torsional muscles have a secondary vertical effect, and the primarily vertical muscles sets have a secondary torsional effect. In upgaze and downgaze the horizontal muscles may have a vertical effect, and the vertical muscles have a horizontal effect. Fortunately most cases of strabismus are not of the highest degrees of complexity!

Treating an imbalance surgically usually involves changing the length and tension of one or both muscles of an agonist/antagonist set. Typically the muscle that is pulling the eye out of alignment is repositioned (recessed) by effectively lengthening it (this changes the eye position) and changing the amount of torque it can generate (the change in torque affects the medium – long-term stability of the new eye position). The 'pair' of the weakened muscle is usually shortened (resected) to pull the eye away from its misaligned position to a more correct one.

How BT-A works in strabismus

Botulinum Toxin type A works by paralyzing the extraocular muscle that is pulling the eye out of alignment. In the initial period of paralysis, there will be an overcorrection of strabismus as the normally functioning antagonist overpowers the paralysed muscle ('the effect'). With this overcorrection there will be contraction of the antagonist and stretching of the paralysed muscle. During this time the lengths of the paralyzed muscle and its antagonist will change, and the length-tension curves within these muscles will also change. Histology shows a change in sarcomere density. When the effect of BT-A wears off, some of these changes will persist, and a resultant net change to the alignment of the eyes occurs ('the after-effect').

For example, in the correction of small angle left convergent strabismus, BT-A is injected into the left medial rectus (LMR). This will paralyze the LMR for some weeks. During that time, the unopposed left lateral rectus (LLR), will abduct the eye, and the eye will be divergent ('the effect'). Whilst the eye is divergent the following changes are likely to occur:

(1) The LMR will be stretched and will lengthen;
(2) The length-tension curve of the LMR will change;
(3) The length-tension curve of the LLR will also change;
(4) The LLR will shorten; and
(5) Sarcomere density in both these muscles will gradually change.

When the LMR paralysis from the BT-A wears off, some of the changes in the lengths and length-tension ratios in both the recently paralyzed and

stretched LMR and the recently contracted LLR will be retained and result in lessened misalignment, 'the after-effect'.

It is important to note that, in this LMR example, BT-A will not have an after-effect if the LLR is not active – a functioning LLR is needed to pull the LMR out and stretch it causing some temporary overcorrection of the misalignment in order to have an after-effect.

The amount of after-effect (change in alignment) will be dependent on the final changes in the lengths of the muscles after the stretching and contraction. The duration of the after-effect (stability of the new alignment) will depend on the changes in the length-tension curves of the muscles and the continuing innervation of these muscles (whether normal or abnormal). If normalized, the changes should be permanent.

Both the quantity and the duration of the after-effect can be augmented by the presence of 'motor fusion', a normal physiological mechanism that successfully converts a symptomatic misalignment or overt strabismus into a latent strabismus. Motor fusion is typically present in all patients with normal childhood visual development. If the motor fusion range ('capture range') is good, the effect on the misalignment will be greater than that which the mechanical effects of the after-effect may have predicted.

How is BT-A given in strabismus

There are number of ways of which BT-A can be administered. The commonest method is by EMG guided injection through a topically anaesthetized conjunctiva in the ophthalmologist's office. A specially designed 27G needle (with the shaft coated, and the tip electrically sensitive) is introduced via the conjunctiva, staying superficial to the sclera to avoid penetration of the globe, approximately 2 cm anterior to the target extraocular muscle (Figure 1). The patient is first asked to look in the opposite direction to the action of the muscle being injected. When the needle is believed to be in the muscle belly, the patient is then asked to look in the direction of action of the extraocular muscle being injected. With this, there will be an increase in the signal output from the EMG, confirming the correct location of the needle. Slow injection of BT-A is then made. The technique should be learnt by watching several live cases.

Other less commonly used techniques of injecting BT-A include:

(1) Injection without EMG guidance ('by feel');
(2) Injection under direct vision into a muscle having surgery to augment the effect of that surgery;
(3) Injection under direct vision through a conjunctival incision prepared just for the BT-A injection;
(4) Injection via subconjunctival lacrimal cannula alongside a muscle [3]; or
(5) Transconjunctival injection after grasping the muscle with forceps and bunching it up [4].

In one series, injection without EMG guidance in 40 children with different types of convergent strabismus has been shown to be reasonably successful with a complication rate comparable to that incurred with EMG guidance [5]. However, when injecting the inferior oblique or inferior rectus muscles, where precision of site of injection is vital to avoid vertical deviations, EMG guidance might be considered to be more important. In patients with multiple previous ocular surgeries and scarring, or with retinal explants after retinal detachment surgery [6,7] or with extremely large globes as in extreme myopia, BT-A injection can be difficult even with EMG guidance.

Some potential patients find the description of a transconjunctival injection in the office to be terrifying and will not proceed for that reason. These patients can be treated after mild midazolam sedation given by an anaesthetist in an ambulatory surgical centre. The patient needs to be sufficiently awake and alert to cooperate with requests to look left, look right, etc.

BT-A in strabismus

Botulinum Toxin type A is most commonly used for horizontal strabismus, including esotropia, exotropia and sixth nerve damage. It may also be used for 4th nerve paresis, vertical deviations, thyroid eye disease

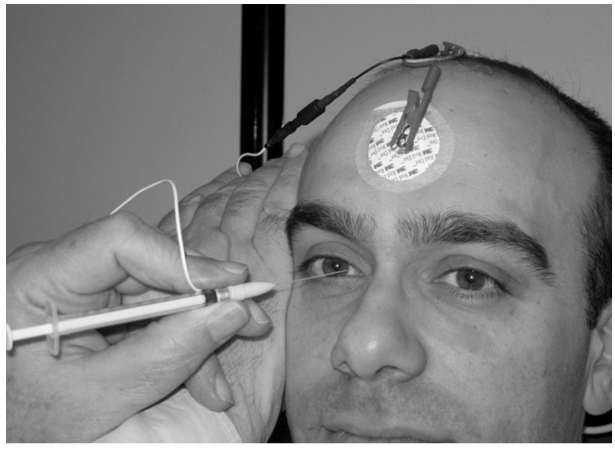

Figure 1. The right medial rectus is about to be injected through the topically anesthetised conjunctiva. A specially designed 27G needle is attached to an EMG machine. An electrode on the patient's forehead is attached to the same machine.

and for diplopia following retinal detachment surgery. Botulinum Toxin injection can also be either diagnostic or therapeutic.

Esotropia (convergent strabismus) and exotropia (divergent strabismus)

Botulinum Toxin type A injection can be used to treat esotropia – injection into the medial rectus, or exotropia – injection into the lateral rectus.

For small to moderate angle esotropia ($<15^{\circ}$), BT-A was found to be as effective as one strabismus surgery in achieving alignment in a study of 236 patients [8] and was shown to be a reliable treatment option in various other studies [9–12]. However, for large angle esotropia ($>15^{\circ}$), BT-A is considered to be less effective [8] and surgery should be considered instead.

In very large angle esotropia ($>30^{\circ}$), it has been shown that surgery [bilateral medial rectus recession] with simultaneous intra-operative BT-A injection into the operated muscle is better than surgery alone [13] (Figure 2a, 2b).

The use of BT-A in exotropia has been less successful than esotropia. Adjustable suture surgery was found to be superior to BT-A injections (in some cases repeat injections were given) [8,9].

Botulinum Toxin type A may also be used to improve an imperfect outcome of horizontal strabismus surgery [14–16]. It is particularly useful in overcorrected exotropia (so-called consecutive esotropia).

The final success of BT-A injection (the 'after-effect') can often be predicted from the initial amount of paralysis and movement deficit produced by the toxin ('the effect'). Gomez de Liano [17] found that a marked movement deficit (=successful paralysis) after BT-A injection was associated with a good alignment outcome in 78% of patients, and a poor movement deficit was associated with a good result in only 17% of patients ($p < 0.001$). Others have also found the movement deficit after BT-A to be predictive of outcome [5,18].

Childhood esotropia and exotropia

Many studies have shown good results in childhood esotropia from BT-A injection to both medial rectus muscles. General anaesthesia is frequently required in these young patients for BT-A injections, although some clinicians will consider performing BT-A injection on swaddled infants using local anaesthetic eye drops in the office.

Bilateral medial rectus BT-A injection for childhood esotropia has shown to have a success rate ranging from 58–89% [19,20–23]. The success rate from a first surgery is at the upper end of this range, so if general anaesthesia is required for the BT-A injection most strabismus specialists will opt for surgery.

The use of BT-A in childhood exotropia has been less extensively researched, but it carries a success rate of 45% or higher [19,24]. The BT-A is injected simultaneously into both lateral rectus muscles.

Negative opinions on use of BT-A in children have been presented. Kushner [25] compared BT-A to surgery in treating infantile esotropia in an editorial comment, and considered that surgery is superior. Ing [26] published data based on a review of 12 patients and considered that BT-A was less effective than surgery when treating congenital esotropia.

The place of BT-A in infantile and later presentation of childhood strabismus has evolved over the last 15 years. Some investigators' results are excellent [20,21,27]. There is no obvious reason why these results cannot be duplicated in other centres.

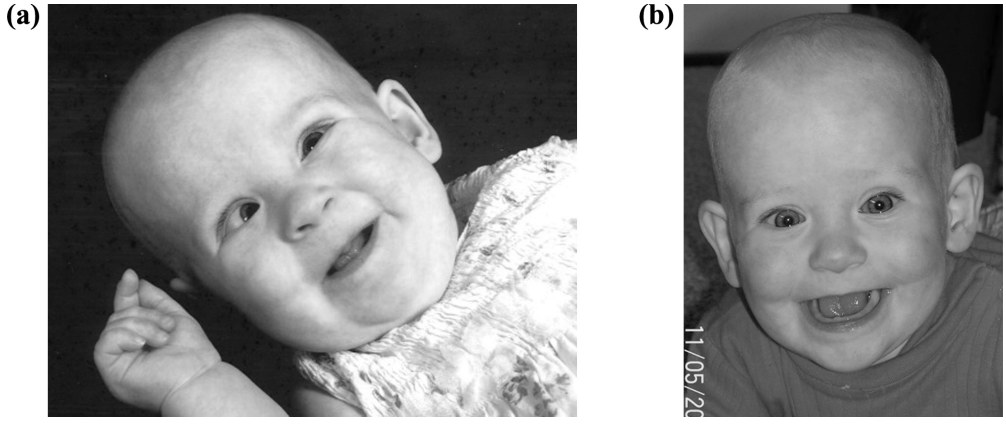

Figure 2. (a) Very large angle esotropia; (b) Six days after surgery augmented by BT-A. Perfectly aligned eyes.

Sixth nerve paresis or palsy

When considering BT-A for sixth nerve palsy it is important to distinguish acute from chronic cases and partial from complete sixth nerve palsies. The following definitions are offered to clarify terminology.

(1) Acute: Recent onset;
(2) Chronic: Of at least 6 months duration;
(3) Partial (=paresis): The LR still has some function;
(4) Complete or total (=palsy): The LR has no function.

In the literature, 'paresis' and 'palsy' tend to be incorrectly used as synonyms.

Acute sixth nerve damage

Earlier BT-A investigators treated acute sixth nerve paresis/palsy with enthusiasm, believing that this prevented medial rectus contracture and resulted in an improved outcome [28–31]. A seminal prospective study by Holmes et al. demonstrated the recovery rates of unilateral traumatic sixth nerve damage to be much higher than previously recognized, with 71% of patients with acute sixth nerve damage demonstrating spontaneous recovery [32,33]. He also reported that 73% of the patients with traumatic sixth nerve paresis treated with BT-A have good post-injection alignment, a result that was not statistically different to the untreated group. Bearing these recent findings in mind, the 'success' of BT-A in treatment of sixth nerve paresis published in some of the older literature must be interpreted with caution.

For patients with acute sixth nerve damage due to microvascular diseases or unknown causes, the Toxin Clinic at the Moorfields Eye Hospital in London found that 80% recover spontaneously whereas 86% of those with BT-A treatment recovered [34]. The difference is not statistically significant, suggesting that prophylactic treatment with BT-A in this group is unnecessary.

There are two further studies of the management of acute sixth nerve damage involving treatment of poorer prognosis groups that warrant specific comment. In one study, 8 patients had nasopharyngeal carcinoma (NPC) [35]. This group of patients are more likely to have other cranial neuropathy (especially first branch of the trigeminal causing corneal anaesthesia), dry eyes and post-radiotherapy ischaemic changes all of which make strabismus surgery more hazardous and BT-A more attractive. In his study, 3 out of 8 patients achieved alignment within 5° [35]. In another study by Wagner et al. [36], eight patients with either tumour or vascular lesions causing sixth nerve palsy were injected within 3 months of onset. Half of these subjects did well.

Chronic sixth nerve damage

These are patients whose acute damage does not spontaneously improve within 6 months of onset. Unfortunately many authors do not accurately distinguish total from partial chronic palsy before drawing a conclusion on the effectiveness of BT-A. In complete sixth nerve palsy, there is absence of lateral rectus function such that when BT-A is injected into the medial rectus, there will be no opposing force to stretch the paralysed muscle. If 'the effect' is small there will be little or no 'after-effect', and so BT-A alone is not expected to have any effect on complete sixth nerve palsy. To assess whether it is a partial or complete sixth nerve palsy, specialized tests are used – forceps force generation tests and saccadic velocity measurements. The degree of movement deficit of the eye or angle of deviation does not reliably segregate these patients.

Studies on this group of patients have given varying results, from infrequent success [37] to frequent success [33]. In this latter group there were successful treatments on patients with large angles of misalignment ($>25^\circ$).

Total sixth nerve palsy

Botulinum Toxin type A treatment alone is not expected to have any lasting effect on complete sixth nerve palsy. However, when combined with transposition surgery (the superior rectus and the inferior rectus are transposed to the upper and lower border of lateral rectus) to provide some lateral pulling force on the medial rectus muscle that has been paralyzed by BT-A injection, excellent results are frequent.

There are 3 excellent and uncannily similar papers on this topic. McManaway et al. [38] found all of 6 patients treated with BT-A and whole tendon transposition had perfect or near perfect alignment, $15–50^\circ$ abduction and $40–100^\circ$ range of single vision. Rosenbaum et al. treated 10 patients similarly [39] and Flanders et al. [40] treated 5; they both found all their patients to have increased field of single vision as well as abducted field of gaze.

Despite this high level of predictability with this technique, as shown by 3 different investigators, it has been largely replaced by a BT-A free technique of 'augmented transposition' where a different suturing technique seems to have largely replaced the BT-A transposition technique without a prospective trial comparing the two techniques [41,42].

Fourth nerve paresis or palsy

The treatment of the persistently underacting superior oblique due to 4th nerve damage often involves surgical weakening the overacting antagonist, the inferior oblique. Botulinum Toxin type A to the inferior oblique provides a useful alternative. Given its close proximity to the inferior rectus, BT-A to inferior oblique needs to be performed under EMG guidance to ensure precise location of injection.

In a study by Buonsanti et al. [43], 20 of 21 injections to the inferior oblique were technically successful. Some 60% of patients, mostly chronic fourth nerve paresis, did well. Six of the chronic fourth nerve damage patients that were aged over 70 did excellently whereas in the under 70 age group, 3 of 6 did poorly. In another study [44], 9 patients with acute fourth nerve damage were injected and all 9 were substantially improved. This study shows that the technique is feasible and safe; however, the results were not compared to the natural history in other similar patients. Despite these studies, the use of BT-A in fourth nerve damage has not become at all popular, even in the hands of BT-A enthusiasts.

Thyroid Eye Disease (TED)

Traditionally, unless the optic nerve or cornea is at risk, Thyroid Eye Disease (TED) is treated medically until it is 'burnt out' before surgical options are considered. During this time, patients often have to endure the unsightly 'startled' face produced by eyelid retraction.

Botulinum Toxin type A has been shown to be effective in correcting upper eyelid retraction during the acute inflammatory stage. One prospective study [45] showed 17 out of 18 patients (94%) had reduction of marginal reflex distance with BT-A injection, whereas another study [46] showed 15 out of 17 eyelids showed some improvements, with 13 patients' upper eyelids returning to normal position. Those who did not improve had retraction duration of >2 years. Repeat BT-A injection every 3 months may be required. This result was supported by another study on 15 patients (21 eyes) where all patients, except one, had improvement with reduction of palpebral fissures after BT-A injection for dysthyroid eyelid retraction [47]. They reported a temporary complication of ptosis in 3 patients and vertical diplopia in 2 patients lasting for less than 1 month. These results showed that BT-A can be considered for use as a temporizing measure before stability for surgery is reached. In the authors' experience, we have not been able to duplicate the particularly good results mentioned above, though we have taken great care to duplicate the published patient selection criteria and BT-A injection technique.

Botulinum Toxin type A is used to treat the diplopia of TED, although published literature on this topic is limited. One study performed by Dunn et al. [48] reported eight patients with TED treated with BT-A, all demonstrated improvement of deviation and four were made diplopia-free. However, in this group, seven patients had disease of less than 8 months duration. Nonetheless, Dunn et al. showed that BT-A is a feasible treatment for patients who are unwilling to wait out the natural history of their disease [48]. The experience from the Toxin Clinic at Moorfields has not been encouraging, whereas that in the Thyroid Clinic at UCSD (San Diego) has been more promising (personal communication).

Chronic use of BT-A

As the 'effect' of BT-A usually wears off within 8 – 12 weeks of injection, if the lasting 'after-effect' is inadequate, repeat injections of patients with BT-A may be desired due to the simplicity of the procedure and patient's preference. A study of 95 patients who have each undergone at least 8 BT-A injections for strabismus demonstrated an overall trend of fewer injections required with time and more importantly, no adverse outcome were found associated with long-term treatment [49]. Long-term administration of BT-A for strabismus is an appropriate treatment option for strabismus patients who do not want to undergo further surgery.

Complications of BT-A treatment

The best source of such information is from the 'Product Information' on Botox® (provided by Allergan; unstated authorship). It contains unpublished data collected by investigators before Food and Drug Authority marketing approval. The complications in 2058 adults who received a total of 3,650 transconjunctival BT-A injections for horizontal strabismus are: Ptosis (16%), acquired vertical strabismus (17%) and spatial disorientation secondary to diplopia or past pointing (no percentage given). On the basis of these data, it would seem that BT-A should not be administered for patients whose eye cannot be patched and still function sufficiently.

Ptosis

Ptosis is a common undesirable complication of BT-A injection. It is presumed to be due to leakage of BT-A through the orbital septum to the levator palpebrae muscle (LPS), paralyzing it and causing

upper lid ptosis. It is common with superior rectus injection (38%) and rarely seen in inferior rectus injections (<1%) [50]. It can also be seen in injection of the horizontal recti where some degree of ptosis was created in as many as 53% of patients and marked ptosis observed in 21% [51]. In a series of 5587 injections of horizontal muscles in 3104 patients the Product Information supplied with Botox® has reported a persistent ptosis rate of 0.3%. Sitting the patient up immediately after the BT-A injection may lower the ptosis rate [52].

Acquired Hypertropias

Acquired vertical deviations following BT-A injection to a horizontal muscle is probably due to leakage of the toxin to either the superior oblique or inferior rectus muscles. Various studies have showed different incidence rates of temporary acquired vertical deviation ranging from 11–78% [11,37,53–58]. When the whole published literature is evaluated, longstanding or even permanent hypertropias are found after 3% of injections but there is a large variation and most investigators report 0%. In a series of 5587 injections of horizontal muscles in 3104 patients the Product Information supplied with Botox® has reported a permanent vertical deviation of $>1^{\circ}$ in 2.1%.

Vision-threatening complications

In this series of 5587 injections of horizontal muscles in 3104 patients the Product Information supplied with Botox® has also reported a number of *vision-threatening complications*. Scleral perforation occurred in 9 patients (0.002%), 1 of these was accompanied by vitreous haemorrhage that spontaneously recovered. Three of the 9 required treatment with either cryotherapy or laser and 6 were untreated. No retinal detachment or visual loss occurred in any of the cases. Retrobulbar haemorrhage occurred in 16 patients and one of these patients required emergency decompression of the orbit in order to restore retinal circulation. None had permanent visual loss. One case of anterior segment ischaemia was reported but the visual outcome of this patient was not provided. These serious vision-threatening complications add up to one in every 300 BT-A injections.

The experience of the Toxin Clinic at Moorfields is very different. A vision-threatening complication has been observed in approximately 1 in 5000 injections (personal communication).

The earlier data probably reflects the complication rate in inexperienced hands, and the UK data the safety of these procedures in experienced hands.

Inadvertent intraocular BT-A injection

One case report of inadvertent intraocular injection of BT-A with complication of inferonasal bullous retinal detachment which required laser treatment around the retinal tear was found [59]. There was initial loss of vision, however, after 2 days the vision returned to 6/6 and remained stable for 5 years. This incidence supports animal studies indicating that intravitreal injection of BT-A does not cause damage to the intraocular tissues.

The future

Botulinum Toxin type A has been used for 20 years in the treatment of many different types of strabismus. It is a useful addition to the therapeutic armamentarium of the ophthalmologist and especially the strabismus specialist. There has unfortunately never been a prospective blinded study to define the precise role(s) of BT-A in different types of strabismus, and much of the current practice is driven by anecdote and small retrospective observational studies. Well designed and controlled prospective studies are needed initially to:

(1) Confirm the types of strabismus where preliminary data suggests that BT-A is likely to be particularly effective, especially for small – moderate angle esotropia of any cause, and fourth nerve palsy;
(2) Identify the types of strabismus where surgery is particularly difficult or the outcome is less predictable, (especially thyroid eye disease and in patients who have had many previous strabismus surgeries) and consider the potential role of BT-A in these groups;
(3) Compare the outcome of transposition techniques augmented with BT-A and those augmented with extra sutures in patients with total sixth nerve palsy.

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References

1. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. Ophthalmology 1980;87(10):1044–1049.
2. Scott AB. Botulinum toxin injection of eye muscles to correct strabismus. Trans Am Ophthalmol Soc 1981;79:734–770.
3. Kao LY, Chao AN. Subtenon injection of botulinum toxin for treatment of traumatic sixth nerve palsy. J Pediatr Ophthalmol Strabismus 2003;40(1):27–30.

4. Mendonca TF, Cronemberger MF, Lopes MC, Nakanami CR, Bicas HE. Electromyograph assistance and Mendonca's forceps – a comparison between two methods of botulinum toxin A injection into the extraocular muscle. Arq Bras Oftalmol 2005 Mar–Apr;68(2):245–249.
5. Chipont E, Garcia-Hermosa P, Arrazola M, Ruiz-Moreno J, Ailò J. Botulinum toxin injection without electromyographic assistance. In: Faber JTD, editor. Transactions 27th Meeting European Strabismological Association; 2001; Florence, Italy; 2001. pp 183–186.
6. Scott AB. Botulinum treatment of strabismus following retinal detachment surgery. Arch Ophthalmol 1990;108(4):509–510.
7. Petitto VB, Buckley EG. Use of botulinum toxin in strabismus after retinal detachment surgery. Ophthalmology 1991;98(4): 509–512.
8. Paul TO, Horn EP, Shepherd R, Dahms GB. Comparison of Botulinum toxin injection to standard strabismus surgery in patients with horizontal strabismus. Presented at the Association for Research in Vision and Ophthalmology, Florida, May 5–10, 2001.
9. Carruthers JD, Kennedy RA, Bagaric D. Botulinum vs. adjustable suture surgery in the treatment of horizontal misalignment in adult patients lacking fusion. Arch Ophthalmol 1990;108(10):1432–1435.
10. Biglan A, Xiao L. Experience with Botulinum A Toxin (Oculinum) in the treatment of strabismus. Contemp Ophthalmic Forum 1987;5:230–240.
11. Balkan RJ, Poole T. A five-year analysis of botulinum toxin type A injections: some unusual features. Ann Ophthalmol 1991;23(9):326–333.
12. Dawson EL, Lee JP. Does Botulinum toxin have a role in the treatment of small-angle esotropia? Strabismus 2004;12(4): 257–260.
13. Khan AO. Two horizontal rectus eye muscle surgery combined with botulinum toxin for the treatment of very large angle esotropia. A pilot study. Binocul Vis Strabismus Q 2005;20(1):15–20.
14. McNeer KW. An investigation of the clinical use of botulinum toxin A as a postoperative adjustment procedure in the therapy of strabismus. J Pediatr Ophthalmol Strabismus 1990; 27(1):3–9.
15. Biglan AW, Burnstine RA, Rogers GL, Saunders RA. Management of strabismus with botulinum A toxin. Ophthalmology 1989;96(7):935–943.
16. Dawson EL, Marshman WE, Lee JP. Role of botulinum toxin A in surgically overcorrected exotropia. J Aapos 1999;3(5): 269–271.
17. Gomez de Liano R. Tratamiento del estrabismo infantil mediante toxina botulinica. Acta Estrabologica 1993:37–42.
18. Dengis C, Martin M, Steinbach J, Kraft S. Botulinum toxin chemodenervation of medial & lateral rectus muscles produces equal shifts of eye alignment for equal degrees of induced paresis. Binoc Vision Eye Muscle Surg Qrtly 1993;9:159–164.
19. Scott A. Botulinum toxin treatment of strabismus. Focal points: Clinical modules for ophthalmologists. Am Acad Ophthalmol 1989:1–11.
20. McNeer KW, Tucker MG, Spencer RF, Scott AB. Botulinum toxin management of essential infantile esotropia in children. Arch Ophthalmol 1997;115(11):1411–1418.
21. Gomez de Liano R. Botulinum toxin in esotropic patients up to 3 years of age. In: Update on strabismus and pediatric ophthalmology. Boca Raton, FL: CRC Press; 1996. p 25.
22. Campos E. Indicazioni e aspettative net trattmento con tossina botulinica. Bollettino do Oculista Anna 1996;75(Suppl.):N4.
23. Scott AB, Magoon EH, McNeer KW, Stager DR. Botulinum treatment of childhood strabismus. Ophthalmology 1990; 97(11):1434–1438.
24. Spencer RF, Tucker MG, Choi RY, McNeer KW. Botulinum Toxin management of childhood intermittent extropia. Opthalmology 1997;104(11):1762–1767.
25. Kushner BJ. Botulinum Toxin management of essential infantile esotropia in children. Arch Ophthalmol 1997; 115(11):1458–1459.
26. Ing MR. Botulinum alignment for congenital esotropia. Ophthalmology 1993;100(3):318–322.
27. McNeer KW, Tucker MG, Guerry CH, Spencer RF. Incidence of stereopsis after treatment of infantile esotropia with botulinum toxin A. J Pediatric Ophthalmol Strabismus 2003;40(5):288–292.
28. Metz HS, Mazow M. Botulinum toxin treatment of acute sixth and third nerve palsy. Graefes Arch Clin Exp Ophthalmol 1988;226(2):141–144.
29. Metz HS, Dickey CF. Treatment of unilateral acute sixth-nerve palsy with botulinum toxin. Am J Ophthalmol 1991; 112(4):381–384.
30. Murray AD. Early and late botulinum toxin treatment of acute sixth nerve palsy. Aust N Z J Ophthalmol 1989;17(3):239–245.
31. Murray AD. Early botulinum toxin treatment of acute sixth nerve palsy. Eye 1991;5(Pt 1):45–47.
32. Holmes JM, Droste PJ, Beck RW. The natural history of acute traumatic sixth nerve palsy or paresis. JAAPOS 1998;2(5): 265–268.
33. Holmes JM, Beck RW, Kip KE, Droste PJ, Leske DA. Botulinum toxin treatment versus conservative management in acute traumatic sixth nerve palsy or paresis. JAAPOS 2000;4(3):145–149.
34. Lee J, Harris S, Cohen J, Cooper K, MacEwen C, Jones S. Results of a prospective randomized trial of botulinum toxin therapy in acute unilateral sixth nerve palsy. J Pediatr Ophthalmol Strabismus 1994;31(5):283–286.
35. Quah BL, Ling YL, Cheong PY, Balakrishnan V. A review of 5 years' experience in the use of botulinum toxin A in the treatment of sixth cranial nerve palsy at the Singapore National Eye Centre. Singapore Med J 1999;40(6):405–409.
36. Wagner RS, Frohman LP. Long-term results: botulinum for sixth nerve palsy. J Pediatr Ophthalmol Strabismus 1989;26(3):106–108.
37. Chuenkongkaew W, Dulayajinda D, Deetae R. Botulinum toxin treatment of the sixth nerve palsy: An experience of 5-year duration in Thailand. J Med Assoc Thai 2001;84(2): 171–176.
38. McManaway JW 3rd, Buckley EG, Brodsky MC. Vertical rectus muscle transposition with intraoperative botulinum injection for treatment of chronic sixth nerve palsy. Graefes Arch Clin Exp Ophthalmol 1990;228(5):401–406.
39. Rosenbaum AL, Kushner BJ, Kirschen D. Vertical rectus muscle transposition and botulinum toxin (Oculinum) to medial rectus for abducens palsy. Arch Ophthalmol 1989; 107(6):820–823.
40. Flanders M, Qahtani F, Gans M, Beneish R. Vertical rectus muscle transposition and botulinum toxin for complete sixth nerve palsy. Can J Ophthalmol 2001;36(1):18–25.
41. Paysse EA, Brady McCreery KM, Ross A, Coats DK. Use of augmented rectus muscle transposition surgery for complex strabismus. Ophthalmology 2002;109(7):1309–1314.
42. Rosenbaum AL. Costenbader Lecture. The efficacy of rectus muscle transposition surgery in esotropic Duane syndrome and VI nerve palsy. JAAPOS 2004;8(5):409–419.
43. Buonsanti J, Sanchez-Covisa M, Scarfone H, Lynch J. Botulinum Toxin chemodenervation of the inferior oblique muscle for chronic and acute IV nerve palsies: Results in 15 cases. Binocular Vis Strab Qrtly 1996;11:119–124.
44. Lozano-Pratt A, Estanol B. Treatment of acute paralysis of the fourth cranial nerve by Botulinum Toxin A chemodenervation. Binoc Vision Eye Muscle Surg Qtrly 1994;9:155–158.

45. Morgenstern KE, Evanchan J, Foster JA, Cahill KV, Burns JA, Holck DE, et al. Botulinum toxin type a for dysthyroid upper eyelid retraction. Ophthal Plast Reconstr Surg 2004;20(3):181 – 185.
46. Boulos PR, Almazroui Y, Hardy I, Wong J, Khouri L. Botulinum toxin type A treatment of upper eyelid retraction in active inflammatory Graves' ophthalmopathy. Invest. Ophthalmol. Vis Sci 2004;45(5):263.
47. Shih M-J, Liao S-L, Lu H-Y. A single transcutaneous injection with Botox® for dysthyroid lid retraction. Eye 2004;18:466 – 469.
48. Dunn WJ, Arnold AC, O'Connor PS. Botulinum toxin for the treatment of dysthyroid ocular myopathy. Ophthalmology 1986;93(4):470 – 475.
49. Horgan SE, Lee JP, Bunce C. The long-term use of botulinum toxin for adult strabismus. J Pediatr Ophthalmol Strabismus 1998;35(1):9 – 16.
50. McNeer KW. Botulinum toxin injection into the superior rectus muscle of the non-dominant eye for dissociated vertical deviation. J Pediatr Ophthalmol Strabismus 1989; 26(4):162 – 164.
51. Burns CL, Gammon JA, Gemmill MC. Ptosis associated with botulinum toxin treatment of strabismus and blepharospasm. Ophthalmology 1986;93(12):1621 – 1627.
52. Stavis M. Ptosis: A preventable side effect following botulinum injection for strabismus. Am Orthoptic J 1985;35:53 – 58.
53. D'Esposito M, Calace P, De Bernardinis T, Cortese G, Sarno G. Ten years of Botulinum Toxin experimentation: Indications and results. Ital J Ophthalmol 1991;5:197 – 201.
54. Flanders M, Tischler A, Wise J, Williams F, Beneish R, Auger N. Injection of type A botulinum toxin into extraocular muscles for correction of strabismus. Can J Ophthalmol 1987;22(4):212 – 217.
55. Flynn JT, Bachynski B. Botulinum toxin therapy for strabismus and blepharospasm: Bascom Palmer Eye Institute experience. Trans New Orleans Acad Ophthalmol 1986; 34:73 – 88.
56. Han SH, Lew H, Jeong CW, Lee JB. Effect of botulinum toxin A chemodenervation in sensory strabismus. J Pediatr Ophthalmol Strabismus 2001;38(2):68 – 71.
57. Szpytma R. Efficacy of Botulinum Toxin A Injection for the treatment of strabismus. Chibret Int J Ophthalmol 1989; 6:33 – 39.
58. Shipman S, Weseley A, Cohen K, Wang F. Secondary vertical deviations after oculinum injection. Am Orthoptic J 1986; 36:120 – 123.
59. Liu M, Lee HC, Hertle RW, Ho AC. Retinal detachment from inadvertent intraocular injection of botulinum toxin A. Am J Ophthalmol 2004;137(1):201 – 202.