REVIEW ARTICLE

Ocular Uses of Botulinum Toxin: An Overview

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Introduction

Botulinum toxin, the most potent poison known (it can be lethal at doses as low as 0.05 µg) has been feared as a possible biological weapon (1). It is produced by the bacterium Clostridium botulinum which produces seven antigen- specific neurotoxins i.e A, B, C, D, E, F, and G (2). Botulinum toxin type A is most commonly utilized for ocular purposes.. Botulinum neurotoxin blocks neuromuscular transmission by antagonizing the serotonin mediated calcium ion release in the peripheral cholinergic nerve endings and thus prevents acetylcholine being released from the presynaptic terminals (3). Thus when injected i.m. at therapeutic doses, botulinum toxin produces a partial chemical denervation of the muscle resulting in localized muscle paralysis. This paralysis is however temporary. Recovery of muscle function often occurs because of axonal sprouting and formation of new neuromuscular junctions (3,4). Botulinum toxin interferes with transmission not only at the neuromuscular junction but also in the cholinergic autonomic parasympathetic and postganglionic sympathetic nervous system. As such it is increasingly found useful in the treatment of various disorders of the autonomic nervous system (5). The potential for a therapeutic use for botulinum toxin was first recognised by Justinus Kerner who in 1817 provided the earliest account of food borne botulism (6). He correctly recognised that the toxin paralysed skeletal muscles and parasympathetic function, and proposed that botulinum toxin could be used as a therapeutic agent. It was not until the 1981 report of botulinum toxin injections into eye muscles to correct strabismus that the therapeutic potential of this agent was fully recognised (7). Its clinical use was spearheaded in ophthalmology where its potential applications have expanded to cover a broad range of visually related disorders. These include strabismus (7-10), nystagmus (11-15), entropion (16,17), headache syndromes such as migraine (18), benign essential blepharospasm(19-20),myokyimia,lacrimal hypersecretion syndromes, eyelid retraction, aberrant regeneration of facial nerve, corneal exposure, compressive optic neuropathy, and, more recently, periorbital aesthetic uses (8,9). However the two main indications are:

Strabismus

When used for the treatment of strabismus, it has been postulated that the administration of botulinum toxin type A affects muscle pairs by inducing an atrophic lengthening of the injected muscle and a corresponding shortening of the antagonist muscle. Alan B Scott and colleagues are credited with first using botulinum type A neurotoxin in strabismus cases ,to temporarily paralyze extraocular muscles thus allowing the antagonists to contract and effect a permanent change in the alignment of the two eyes.7 The toxin may be injected in conscious patients , with the syringe needle connected to an auditory myogram device that amplifies the muscle action potentials; on successful injection the action potential disappears and the muscle becomes silent. The muscle may also be injected under direct visualization and a general anaesthetic. Injection without surgical exposure or electromyographic guidance should not be attempted. Currently it is being used in treatment of strabismus in patients 12 years of age or older though it has also been successfully used in children as young as 9 years of age.

Indications

- -Patients who are not fit for surgery e.g because of some illness, history of malignant hyperthermia etc
- -Patients who refuse surgery
- -Patients who have had multiple strabismus surgeries previously
- -Patients with acute sixth nerve palsy with mild esotropia

Relative Contraindications (5,8)

- -Deviations over 50 prism diopters
- -Restrictive strabismus (i.e due to presence of scar tissue or entrapment of tissue)
- -Duane's syndrome with lateral rectus weakness
- -Chronic paralytic strabismus

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Biglan *et al* (10) reported best results with botulinum toxin in patients who had surgical overcorrections(87.5% success) and mild sixth nerve palsy (43.7% success) and worst results in patients with comitant exotropia and infantile esotropia(13.35 and 33.3% controlled respectively.

Dosage of Botulinum Toxin Type A to be used in Strabismus

Before injecting botulinum toxin type A, several drops of a local anesthetic and an ocular decongestant should be instilled in the eye a few minutes prior to injection.

Initial Dose (8)

1) ***Horizontal strabismus***
   < 20 prism diopters: 1.25 to 2.5 U in any one muscle.
   20 to 50 prism diopters: 2.5 to 5.0 U in any one muscle
2) ***Vertical strabismus***
   1.25 to 2.5 U in any one muscle
3)***. Persistent VI nerve palsy***
   1.25 to 2.5 U in the medial rectus muscle of 1 month

Lower doses should be used for treatment of small deviations.Larger doses should be used only for large deviations. The recommended volume of botulinum toxin type A injected for treatment of strabismus is 0.05 to 0.15 mL per muscle.The above mentioned doses of the diluted botulinum toxin type A typically create paralysis of injected muscles beginning 1 to 2 days after injection and increasing in intensity during the first week. The paralysis lasts for 2 to 6 weeks and gradually resolves over a similar time period. About one-half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

Subsequent doses for residual or recurrent strabismus (5,8)

1) Patients should be re-examined 7 to 14 days after each injection to assess the effect of that dose.
2) Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
3) Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to 2-fold compared to the previously administered dose.
4) Subsequent injections should not be administered until the effects of the previous dose have dissipated
5) The maximum recommended dose as a single injection-25U

Ocular Adverse Reactions and Complications(8)

a) Lack of response: due to inadequate dose selection, selection of inappropriate muscles for injection, muscles inaccessible to injection, underlying structural abnormalities such as muscle contractures or bone disorders, change in pattern of muscle involvement,inappropriate storage or reconstitution, as well as neutralizing antibodies to botulinum toxin.

b) Spatial disorientation, double vision.

c) Ptosis or vertical deviation 15.7 and 16.9%

d) Scleral perforation and retrobulbar hemorrhage.

e) Adies pupil due to ciliary ganglion damage.

f) Anterior segment ischemia.

Benign Essential Blepharospasm (BEB)

The initial treatment of choice for benign essential blepharospasm is chemodenervation of the orbicularis oculi muscle with botulinum toxin type A(19,20).Often the procerus and corrugator muscles are also involved and thus require injection.The toxin can be injected without electromyographic guidance in cases of BEB. It is injected into the medial and lateral pretarsal orbicularis oculi of the upper lid and into the lateral pretarsal orbicularis oculi of the lower lid. 95-98% patients of BEB show adequate response to this toxin (3).

Dosage of Botulinum Toxin Type A in BEB

1) The initial recommended dose is 1.25 to 2.5 U per injection s site (0.05 to 0.1 mL volume at each site). The initial effect of the injections is seen within 24-72 hrs, with a plateau usually at 3-5 days, but occasionally the effect may be delayed as long as 2-4 weeks (2,20,21) Treatment effects last approximately 3 months, following which the procedure can be repeated
2) At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient.However there is little benefit obtainable from injecting more than 5 units per site.
3) The toxin should not be given more frequently than once every 3 months to prevent antibody formation and subsequent failiure with treatment.
4) The cumulative dose in a 2-month period should not exceed 200 U when used for the treatment of BEB .
5) If no response occurs to botulinum toxin type A after repeated injections and antibodies to it are detected , then another antigenically distinct serotype of the toxin e.g type F may be helpful .

Ocular Adverse Reactions and Complitaions

1) Corneal exposure, persistent epithelial defects and corneal ulceration, especially in patients with VII nerve disorders.
2) Ptosis (migration of the toxin below the orbital septum-causing paralysis/paresis of the levator muscle(11%).
3) Irritation/tearing because of dry eye, lagophthalmos, and photophobia may occur in upto 10 %.
4) Ectropion, diplopia and entropion may occur though their incidence is very less(less than 1%).
5) Occurrence of acute angle closure glaucoma in a patient one day after receiving an injection of botulinum toxin for blepharospasm has also been reported.
6) Ecchymosis of the lids .

Nystagmus: Acquired nystagmus (seen in neurological diseases like multiple sclerosis) is often associated with impaired visual function, due to excessive movement of retinal images (11) Failure of the visual cortex to adapt to nystagmus results in oscillopsia, which may be incapacitating(12). Producing external ophthalmoplegia by retrobulbar injection of botulinum toxin as a treatment for acquired nystagmus was first described in 1988,(13) Repeated injections are required to maintain therapeutic effect, and entail the risks of retrobulbar haemorrhage, damage to orbital contents, ptosis, and diplopia(14,15). Inadvertent intravascular injection of toxin however, appears to be of little significance, the dose being insufficient to produce systemic toxicity.

Entropion: Botulinum toxin has been used safely for the treatment of spastic and congenital entropion(16), by injection into the pretarsal portion of the orbicularis oculi muscle (5 U). There are also reports of it being used to treat senile entropion (17), though in this case the effect is temporary and surgery remains the definitive treatment of choice.

General Precautions to be taken when using Botulinum Toxin type A

1) The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics, or other drugs that interfere with neruromuscular transmission (e.g., tubocuraine-type muscle relaxants) .A detailed drug history should therefore be elicited before injection of the toxin .
2) Caution should also be exercised when botulinum toxin type A is utilized for treatment of patients with myasthenia gravis, Eaton Lambert Syndrome, or other disorders that produce a depletion of acetylcholine.
3) As with all biologic products, an anaphylactic reaction may occur. Necessary precautions should be taken and epinephrine should be available.
4) There are no adequate and well-controlled studies of botulinum toxin type A administration in pregnant women or of its excretion in human milk. Thus caution needs to be exercised in pregnant and lactating women.
5) Safety in children below the age of 12 years has not been established.
6) Patients who are sedentary should be cautioned to resume activity gradually following its administration.

References

1 Arnon SS, Schecter R, Inglesby TV, *et al.* Botulinum toxin as a biological weapon. Medical and public health management. *JAMA* 2001;285:1059-70

2 Gonnering RS.Pharmacology of botulinum toxin.*Int Ophthal Clin* 1993; 33: 203- 27

3 Dutton JJ. Acute and chronic, local and distant effects of botulinum toxin. *Surv Ophthalmol* 1996;40: 51-65.

4 Holds JB, Fogg SG, Anderson RL. Motor nerve sprouting in human orbicularis muscle after botulinum A injection. *Invest Ophthalmol Vis Sci* 1990; 31:964-67.

5 Naumann M , Jost W, Toyka KV. Botulinum toxin in the treatment of neurological disorders of the autonomic nervous system. *Arch Neurol* 1999;56:914-16

6 Erbguth FJ, Naumann M. Historical aspects of botulinum toxin. Justinus Kerner (1786-1862) and the "sausage" poison. *Neurology* 1999;53:1850-53.

7 Scott A. Botulinum toxin injection of eye muscles to correct strabismus. *Trans Am Ophthalmol Soc*1981; 79: 734-70

8 Dutton JJ, Fowler AM. Botulinum toxin in ophthalmology. *Surv Ophthalmol* 2007; 52:13-31.

9 Osako M, Keltner. Botulinum A toxin (Oculinum) in ophthalmology.*Ophthalmol* 1991;36:28-46.

10 Biglan A, Burnstine R, Rogers G, *et al.* Management of strabismus with botulinum A toxin. *Ophthalmology*1989; 96: 935-43.

11 Menon G J, Thaller VT. Therapeutic external ophthalmoplegia with bilateral retrobulbar botulinum toxin,? an effective treatment for acquired nystagmus with oscillopsia. *Eye* 2002 16, 804-06

12 Evans N. Treacher Collins prize essay. The significance of nystagmus. *Eye* 1989; 3: 816-32.

13 Helveston EM, Pogrebniak AE. Treatment of acquired nystagmus with botulinum A toxin. *Am J Ophthalmol* 1988; 106: 584-86.

14 Repka MX, Savino PJ, Reinecke RD. Treatment of acquired nystagmus with botulinum neurotoxin A. *Arch Ophthalmol* 1994; 112: 1320-24.

15 Ruben ST, Lee JP, O'Neil D *et al.* The use of botulinum toxin for treatment of acquired nystagmus and oscillopsia. *Ophthalmology* 1994; 101: 783-87.

16 Christiansen G, Mohney BG, . Baratz KH, *et al.* Botulinum toxin for the treatment of congenital entropion. *Am J Ophthalmol* 2004;138:153-55

17 Clarke JR, Spalton DJ. Treatment of senile entropion with botulinum toxin. *Br J Ophthalmol*1988; 72: 361-62.

18 Ashkenazi A , Silberstein SD. Botulinum toxin and other new approaches to migraine therapy. *Annu Rev Med* 2004;55:505-18

19 Patrinely JR, Anderson RL. Essential blephrospasm: A review. *Geriatr Ophthalmol* 1986; 32:23-25

20 Dutton JJ, BuckleyEG. Botulinum toxin in the management of blepharospasm. *Arch Neurol* 1986 ; 43 : 380-82.