BOTULINUM TOXIN: A POISON FOR SOME, A POTION IN OCULOPLASTICS

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INTRODUCTION

Botulinum A toxin is a potent neurotoxin produced by the bacterium Clostridium botulinum. It is responsible for the causation of both adult and infantile forms of botulism, which can be potentially life threatening. Botulism is contracted via contaminated food or wounds.

Botulinum A toxin blocks transmission at cholinergic synapses by impairing quantal acetylcholine release at motor nerve endings[2] and leads to paralysis of many systems including extra-ocular muscles, facial, bulbar, respiratory, limb and gastrointestinal musculature.

Nonetheless, despite its toxicity, low doses of botulinum toxin under controlled conditions may be of tremendous benefit to the Oculolplastic patient. Oculoplastics, a sub-specialty of Ophthalmology, encompasses the management of a wide range of reconstructive and aesthetic patients with eyelid, lacrimal and orbital disorders.

PHARMACOLOGY OF BOTULINUM A TOXIN

There are 8 antigenically distinct serotypes (A, B, C1, C2, D, E, F and G) of botulinum toxin[1], but only type A has been used clinically. All of them share a similar chemical structure with a light chain and a heavy chain linked by disulfide bond. Botulinum A toxin (Botox, Allergan, Irvine, CA) is now commonly used in Singapore.

Botox is supplied in a frozen, sterile, lyophilised form in a vial of 100 units (Figure 1). The product is stable for up to 4 years[3] if properly stored. It is used as a solution for injection by mixing the vial contents with the unpreserved saline supplied by the manufacturer. Once diluted, the solution will deteriorate within a few hours[4]. It is therefore not advisable to store Botox solutions overnight for reuse as its efficacy diminishes with time. The solution is best used when freshly prepared on the day of dilution, preferably immediately after dilution. If Botox is to be shared among a few patients, it is helpful to schedule them to be done in the same day within a short time frame.

In addition, the unstable toxin molecules may be damaged by factors such as heat, chemicals, pH and mechanical forces (such as shaking). The dilution should be done in a gentle and atraumatic manner. The amount of saline used for dilution is dependant on the concentration of the injection desired by the physician.

The paralytic action of the toxin is dose-dependant with a maximal effect achieved in 5 to 7 days after injection[3]. However, the onset of action may differ from one patient to another and from one injection site to another. The duration of action is also variable. Complete recovery of muscle function has been stated to occur after 6 to 9 months[5], but I have seen effects lasting as short as 6 weeks to 3 months. Recovery occurs with the formation of new sprouting from nerve endings at the neuromuscular junction[3]. This may explain the variability of the effect of the toxin. Occasionally, the injected muscle may not recover full pre-injection function.

One concern is the development of tachyphylaxis[6] with long-term use of Botox. In this instance, the patient gradually requires higher subsequent doses to achieve the same desired effect. This is however, very rare in practice and in fact, one author reported that the duration of spasm-

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free intervals increased with subsequent injections[7]. However, it should be noted that muscle spasm is a subjective measurement parameter. Some patients may complain of residual spasm even in the objective presence of orbicularis weakness.

MEDICAL USES OF BOTULINUM A TOXIN IN OCULOPLASTICS

Botulinum toxin is a useful therapeutic agent in the Oculoplastic clinic for many spastic disorders. The details of the dose and injection sites for each of the conditions treatable by this drug will not discussed here. Readers are encouraged to refer to specialised plastic surgery or Oculoplastic surgery textbooks for further information.

1. Essential blepharospasm

Essential blepharospasm is a progressive, repetitive, involuntary forceful closure of the eyelids due to spasmodic contraction of the orbicularis oculi muscles (Figure 2). It occurs more commonly in women than men. It is usually a bilateral condition and may be associated with dyskinesias of other muscle groups such as facial muscles, neck, jaw and soft palate. The latter may manifest as facial grimacing, contraction bands in the neck, lip pursing, mouth opening, dysarthria and dystonia. The combination of blepharospasm and lower facial dystonia is called Meige's syndrome (Figure 3). The spasms usually resolve during sleep. The diagnosis is clinical and neuro-imaging is generally not required. The etiology is unknown, although it has been postulated to be a rostral brain stem/ basal ganglion disease. In severe cases, the patients become functionally blind because of tonic closure of the eyelids obviating vision and affecting their activities of daily living. Depression may occur necessitating psychiatric management.

Essential blepharospasm has been treated with

Figure 1: Botulinum A toxin in the form of a 100 unit vial (Botox, Allergan, Irvine, CA).

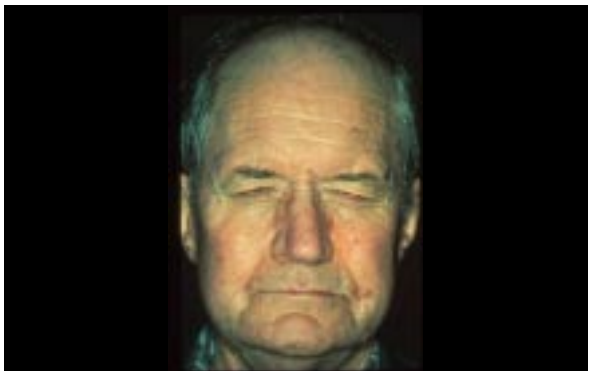

Figure 2: Essential blepharospasm seen as isolated spasmodic contraction of both eyelids (orbicularis oculi muscles).

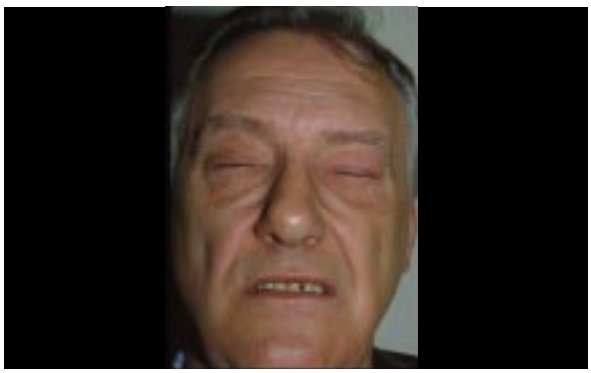

Figure 3: Meige's syndrome. Spastic contraction of both eyelids (essential blepharospasm) and lower face (evident as contraction of the levators of the upper lip).

various modalities of treatments with variable success. The treatments include pharmacotherapy (eg. Clonazepam, diazepam, benzhexol), hypnotherapy, psychotherapy, acupuncture, thermolysis of the facial nerve, Botox injection and surgery. The latter consists of neurectomy (of the facial nerve) and myectomy (partial or complete excision of the orbicularis oculi muscle). The optimal treatment for this condition is still unknown. Botox injections to the upper eyelid, lower eyelid, brow, lateral canthal area and lower face have been used with very good success in many but not all patients[8,9]. Surgery is generally reserved for recalcitrant cases that have failed Botox treatment. For cases with residual spasm that require post-operative Botox injections after neurectomy/myectomy, the surgery itself seem to prolong the spasm-free period offered by Botox[10]. Meige's syndrome can be more difficult to treat than essential blepharospasm with shorter spasm-free intervals after Botulinum toxin injections[7,11].

2. Hemifacial Spasm

In contrast to essential blepharospasm, hemifacial spasm is characterised by unilateral intermittent, tonic contraction of the facial muscles that persist during sleep (Figure 4). It rarely occurs bilaterally. The spasm usually starts in the orbicularis oculi muscle and spreads to the rest of the facial muscles. It may be associated with ipsilateral facial nerve weakness. There is a predilection for females and occasional familial cases have been reported[12]. This condition should be differentiated from essential blepharospasm as the management is different. Unlike the latter, magnetic resonance imaging is advisable since some hemifacial spasms can be due to facial nerve root compression by an ectactic blood vessel or rarely by a tumor such as pontine glioma or cerebello-pontine angle tumor[13]. The ecstatic vessels that are implicated include anterior inferior cerebellar artery, posterior inferior cerebellar artery and the internal auditory artery. In these cases, neurosurgical decompression of the facial nerve may be curative. Botulinum type A toxin injection is a good treatment option for patients with residual spasm after surgery or those who were treated conservatively because they refuse surgery or are poor surgical candidates.

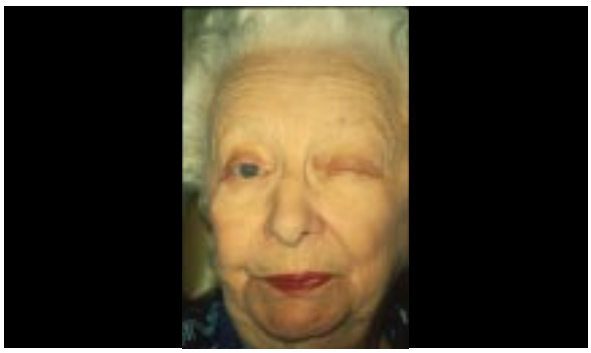

Figure 4: Hemifacial spasm. Unilateral, intermittent contractions of the facial muscles.

3. Aberrant regeneration of the facial nerve

This neurological disorder may occur after Bell's palsy or facial nerve trauma. It occurs as a result of misdirection of the facial nerve sprouting to other cranial nerves (such as the trigeminal nerve) during the recovery phase. It manifests as anomalous movements such as eyelid closure, twitching or spasm with the use of lower facial musculature. It can be a disturbing and cosmetically unacceptable situation for the patient. Botulinum type A toxin is an effective treatment of this condition[14,15].

4. Myokymia (eyelid twitching)

This benign, self-limiting condition may affect the upper or lower eyelid of healthy individuals not uncommonly. The cause is unknown but has been attributed to stress. It is important to differentiate it from facial myokymia. The latter presents as

continuous, involuntary, spasmodic movements of the facial muscles and may be caused by brain stem tumors or multiple sclerosis[16]. The patient is generally given reassurance and managed conservatively. Botulinum toxin has been used with some success[17] and should be reserved only for persistent symptomatic patients.

5. Other disorders

Other disorders in which Botulinum toxin may have an effect but a less well-established role include the following:

a. *Lower lid entropion*
Spastic entropion (in turning of the eyelid margin) occurs as a result of some irritants, such as misdirected eyelashes (trichiasis) or corneal disease acting on eyelids predisposed to developing entropion. These eyelids commonly have underlying age-related degenerative changes such as lower eyelid retractor dehiscence and horizontal lid laxity[18]. The definitive treatment of spastic entropion in such eyelids should be surgery. The entropion surgery generally involves a lower eyelid incision to reattach the lower eyelid retractor with the addition of a lid tightening procedure[18] (lateral tarsal strip procedure) if indicated. Nonetheless, botulinum toxin may have a limited, temporising role[19,20] in a patient who is unfit or refuses surgery. Everting (Quickert's) sutures also have a similar temporising effect.

b. *Persistent corneal epithelial defect/ ulceration*
Tarsorrhaphy (surgical adherence of the upper and lower eyelid) has been the gold standard to effectively treat non-healing corneal epithelial defect/ulceration. Kirkness et al[21] has however, advocated a medical/pharmacological tarsorrhaphy by inducing ptosis (droopy upper lid) with botulinum injection into the levator muscle. This chemodenervation technique offers the advantages of being less invasive, reversible, no damage to the lid margin, the ease of eye examination and eye medication instillation in the ptotic eye. They have reported a 90% success with the healing of indolent corneal ulcers. Nonetheless, it is difficult to be certain that the botulinum toxin injection is delivered only to the levator muscle alone without paralysing the nearby superior rectus.

Paralysis of the latter results in vertical diplopia, an undesired side effect that will take weeks to recover, although it tends to recover faster than the lid[21].

c. *Subacute dysthyroid myopathy*
Graves disease may be associated with diplopia due to involvement of the extra-ocular muscles. Squint surgery is frequently required in the later stages of the eye disease to correct diplopia due to restrictive myopathy from fibrosis of the muscles. In the acute stage, surgery is contra-indicated in view of the active orbital inflammation and unpredictable surgical results. Botulinum toxin has been used in this interim to treat ocular misalignment and to relieve diplopia with success by some authors[22,23]. In the chronic stage, the fibrotic muscles will not respond to Botulinum injection and will require surgical correction.

In ophthalmology, botulinum has also been used in the treatment of non-paralytic vertical and horizontal squints; acute/chronic third and sixth nerve palsies and squints following retinal detachment or squint surgery. Helveston et al[24] has also used it to manage ocillopsia (perception of jerky images) and diminished vision due to nystagmus.

COSMETIC USES OF BOTULINUM A TOXIN IN OCULOPLASTICS

Recently, Botulinum A toxin injections have emerged as a popular treatment for dynamic facial wrinkles/rhytides in aging patients. It offers the benefits of being a minimally invasive, reversible, office-based, safe and effective procedure. Its effect in smoothening wrinkles has been observed during the treatment of facial spastic disorders.

Wrinkles occur because of age-related changes. Histopathologically, wrinkles are characterised by many alterations[25] in the skin that include thinning of the epidermis, decrease in many markers of epidermal differentiation (eg. keratohyalin granules), abnormal desquamation, reduced hydrophilic capacity of the horny layer, decreased collagen types IV and VII at the dermo-epidermal junction and diminished chondroitin sulphates in the papillary dermis. Hyperfunctioning facial muscles worsen these facial lines.

There are many types of wrinkles – dynamic facial lines and static wrinkles that include sleep creases, gravitational redundancy and facial lines due to loss of elasticity. Not all wrinkles are treatable by Botox, only dynamic lines due to facial muscle contractions are. Dynamic wrinkles develop perpendicularly to the force of muscular contraction. Botox works by causing temporary muscle relaxation, thus preventing the formation of dynamic, hyperkinetic facial lines. It has been postulated that repeated creasing of the skin may induce changes in the deeper dermis to result in the formation of wrinkles at rest[26]. Thus, Botox has been also been suggested to help prevent the onset or progression of static wrinkles secondary to chronic facial animation and contraction.

The types of dynamic wrinkles that can be softened by Botox injections[27-29] include the following:

1. *Forehead Wrinkles/ rhytides (Frown lines)*
   These horizontal lines develop from repeated contractions of the frontalis muscle (Figure 5).
2. *Gabellar folds*
   These result from repeated contractions of the forehead muscles. The vertical folds are from the corrugators and the horizontal ones from the procerus contractions (Figure 6).
3. *Lateral periocular rhytides/"crow's feet"*
   These occur as a result of contractions of the orbicularis oculi muscle.
4. *Bunny lines*
   These are radial lines that fan across the nose bridge due to the action of the upper nasalis muscle.
5. *Melomental folds*
   These are vertical folds that extend from the upper border of the side of the nose (lateral

Male 36 years old

Before *After*

Figure 5: Horizontal frown lines due to frontalis muscle contraction seen before (left) and after (right) Botox injections. Note the marked improvement after the injections.

Male 42 years old

Before *After*

Figure 6: Gabellar folds due to contractions of the corrugators and procerus muscles seen before (left) and after (right) Botox injections. Botox has markedly improved the wrinkles.

nasal ala) to the lateral angle of the mouth. They develop from contractions of the lip elevator muscles (eg. Levator labii superioris), zygomaticus and risorus muscles.

6. *Vertical lip/ perioral rhytides/"Smoker's lines"*
These cosmetically unacceptable lines radiate from the lip outwards and are secondary to the action of the orbicularis oris muscles. Other contributing factors to these include thinning of the vermilion border of the upper lip, lengthening of the philtrum (area between the nose and the upper lip), elongation and in rolling of the vermillon border of the lip. These complex wrinkles frequently require Botox injections in conjunction with other treatments such as chemical peels and soft tissue augmenting agents like collagen or autologous fat.

7. "*Mouth frown*"
This refers to a sad-appearing, downward angulation of the outer corner of the mouth caused by downward contraction of the depressor anguli oris muscle and upward pulling of the zygomaticus major and minor muscles.

8. *Mental crease*
This is a semi-lunar groove occurring between the lower lip and the chin prominence and is made obvious with contraction of the mentalis muscle.

9. *Horizontal necklace lines*
These are horizontal lines that occur as a result of subcutaneous muscular aponeurotic system (SMAS) attachments in the neck. SMAS is a wide sheet of connective tissue facia that span from the zygoma across the lower face to the neck and is tightened or plicated in facelift surgeries.

10. *Vertical platysma bands*
Aging results in separation of the platysma muscles into 2 bands with an increase in submental fat. The anterior border of these two platysma bands may become visible during neck animation such as playing a musical instrument or speaking. Botox injections may help only in selected cases with good skin tension and minimal submental fat descent.

Other treatment modalities used in the treatment of skin wrinkling include laser resurfacing (eg. With CO_2, erbium-YAG lasers), chemical peels (eg. phenols, glycolic acid), soft tissue fillers (eg. collagen, silicone, autologous fat pearls). Laser and chemical peels incur risks such as hypo- or hyperpigmenatation, scarring, skin infection and persistent erythema, while the fillers may be associated with the problems like visibility of the fillers, resorption, rejection, extrusion and fibrosis. Botox is generally safer compared to these other options but is not appropriate in all cases. For example, deep wrinkles with acne scars may be better treated with laser resurfacing or deep chemical peels. The use of Botox in the cosmetic should be individualised and tailored to the needs of the patient. In addition, the cosmetic patient may be advised to retard the onset of wrinkles by avoiding unprotected sun exposure, smoking, unnecessary facial movements, and certain sleeping positions.

11. *Other cosmetic uses*
Botulinum toxin has also been in cases of brow asymmetry, brow shape contouring and hypertrophied orbicularis oculi. Brow asymmetry due to facial nerve paralyis / injury

can be treated by Botox injections to the normal brow, in order to drop it to match the ptotic/droopy brow in patient decline surgical elevation. Similarly, patients with flat brow contours can be made more aesthetically pleasing by Botox injections to the medial brow to induce mild ptosis/droopiness to create a more curved eyebrow. In rare instances when patients complain of bulginess of the lid margin due to hypertrophied orbicularis oculi muscles, the prominence can be reduced by relaxation of the muscles with direct Botox injections.

Side effects and complications of Botulinum toxin injection

Botulinum type A toxin injections is generally a safe procedure with few side effects and complications in experienced hands. The type of side effect depends on the site and dose of injection. The side effects observed are: ptosis (due to paralysis of the levator), horizontal and/or vertical diplopia (due to paralysis of the extra-ocular muscles), pupillary dilation (due to effect on dilator pupillae) and undesired weakness of adjacent facial muscles (eg. causing facial asymmetry). Complications are uncommon and usually minor and include pain, bruising and hematoma at injection sites. Scleral perforation is extremely rare[30] and its reported occurrence was in a highly myopic patient treated for squint by botulinum injection.

CONCLUSION

Botulinum A toxin is an important and efficacious drug that broadens the therapeutic armamentarium of the Oculoplastic Surgeon. Its safety and reversibility are definite advantages to account for its wide applications both medically and cosmetically.

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