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### RESEARCH ARTICLE

#### BOTULINUM TOXIN- AN ALLROUNDER IN THE OPHTHALMOLOGIST'S PHARMACOPOEIA.

**Fahad AL wadaani.**

King Faisal University Eastern Province PO Box 2247 Zip Code 31982.

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#### Abstract

Botulinum toxin acts by interfering with neural transmission at the neuromuscular junction, causing muscle paralysis. It has been used for a variety of medical conditions like strabismus, hemifacial spasm, and various spastic movement disorders, headaches, hypersalivation, hyperhidrosis etc. It has been used in the field of cosmetology for the treatment of wrinkles and folds. Botulinum toxin represents a simple, safe and cheap alternative to complex surgeries in a number of ophthalmological conditions.

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#### Introduction:-

Botulinum toxin is an exotoxin produced by the Gram positive bacteria, *Clostridium botulinum*.<sup>1</sup> It acts by interfering with neural transmission at the neuromuscular junction, causing muscle paralysis.<sup>2,3</sup> Scott used Botulinum toxin for the first time in 1973 to treat strabismus and it was used on humans in the 1980s. It has been used for a variety of medical conditions like strabismus, hemifacial spasm, and various spastic movement disorders, headaches, hypersalivation, hyperhidrosis etc. It has been used in the field of cosmetology for the treatment of wrinkles and folds.<sup>2,3</sup> The use of Botulinum toxin A was approved by the USFDA for the treatment of strabismus, hemifacial and blepharospasms in 1989, neck problems in 2000 and hyperhidrosis in 2004. In ophthalmology, Botulinum toxin represents a simple, safe and cheap alternative to complex surgeries in a number of conditions.

There are 8 antigenetically distinct types of exotoxins elaborated by *Clostridium botulinum* (A, B, C1, C2, D, E, F and G), of which type A is the most most and most frequently used clinically. The toxin is thought to act by inhibiting the release of acetylcholine from the presynaptic nerve endings at the neuromuscular junction. It is postulated that this action involves binding of this toxin to the presynaptic nerve membrane followed by lysis of SNAP 25 protein which is required for successful docking and release of Acetylcholine from the vesicles in the presynaptic nerve terminal.<sup>3</sup> It is thought to act at multiple sites like the neuromuscular junction, autonomic ganglia, postganglionic parasympathetic nerve endings and postganglionic sympathetic nerve endings that release acetylcholine. The action of Botulinum toxin at the affected terminals is permanent, activity is regained by sprouting of new nerve terminals, which usually takes 2 or 3 months.<sup>2</sup>

The biological effect of Botulinum toxin is expressed in units (U). One unit of botulinum toxin is the amount of toxin that is lethal in 50% of female swiss- Webster mice following intraperitoneal injection (LD 50).<sup>4</sup> The serotype A of Botulinum toxin is most commonly used and the most common preparations are Botox and Dysport. Botulinum toxin is usually injected into the muscle or gland using a 30 G needle, although some ophthalmologists prefer to do it under EMG (electromyograph) monitoring. Its effect starts within 24- 72 hours and reaches a peak effect in 7-14 days.<sup>2</sup>

**Corresponding Author:- Fahad AL wadaani.**

Address:- King Faisal University Eastern Province PO Box 2247 Zip Code 31982.

**Uses In Ophthalmology:-**

The uses of Botulinum toxin in Ophthalmology are myriad and especially related to the ocular motor system.

**STRABISMUS**

Botulinum toxin was used for the first time in the eye for the treatment of strabismus.<sup>5</sup> It was approved in 1991 by the FDA for the treatment of strabismus, blepharospasm and oculomotor palsy.<sup>6</sup> The mechanism of action of Botulinum toxin is by weakening the antagonist muscle, and thus reducing the deviation. Generally, it can be used as an alternative to surgery in non restrictive strabismus like small to moderate angle infantile esotropia, acute esotropia, post surgical residual and consecutive esotropia, and 6<sup>th</sup> nerve palsy.<sup>7,8,9,1</sup> Other indications include patients with strabismus who cannot tolerate general anesthesia and cases with unpredictable surgical results like partially accommodative esotropias, esotropias in cerebral palsy and Thyroid eye disease. It has also been used in management of vertical deviations and nystagmus. It has also been used as a safe alternative to surgery in selected cases of Duane's retraction syndrome.<sup>10</sup> The advantages over surgery include lesser invasiveness, requirement of lesser degrees of anesthesia and decreased chances of muscle fibrosis. Diagnostically, it has been used as a postoperative diplopia test.<sup>11,12</sup> It is also used for temporary relief of diplopias of any cause. Botulinum toxin injections into the Lateral Rectus muscle is considered a promising treatment to improve the fusional control and far and near deviations in patients with intermittent exotropia.<sup>13</sup> It may also be used in the management of adult convergence insufficiency.<sup>14</sup> For strabismus, the average dose of Botulinum injection is 1-3 U/muscle<sup>1</sup> Complications include ptosis, acquired deviations and greater propensity of undercorrections, but this procedure is still very popular due to its less traumatic nature.

**Blepharospasm And Other Muscle Spasms:-**

Essential blepharospasm is a condition characterized by involuntary eye closure due to recurrent, forceful contractions of the Orbicularis oculi muscle.<sup>15,16</sup> This can lead to prolonged closure of the eyelids and visual impairment. Dry eye disease is often reported as an association and recent studies implicate the blepharospasm for dry eye. Normal eyelid blinking plays a vital role in the maintenance of a healthy, precorneal tear film and patients with blepharospasm are likely to have an unstable tear film. Botulinum toxin A injection is the first line in the management of Essential blepharospasm. It helps to control the spasms by its action on the Orbicularis oculi muscle. It also helps to relieve the headache and ocular pain seen in patients suffering from blepharospasm and hemifacial spasm.<sup>17</sup> The dosage ranges from 12.5-25 U of Botox. Botulinum toxin is postulated to relieve the associated dry eye symptoms by stabilizing the precorneal tear film and improving the ocular surface by reducing the blinking frequency and reduced tear excretion by its action on the lacrimal pump.<sup>15</sup> Some studies have reported a dramatic improvement in the ocular surface and improvement in higher order aberration with this treatment although other studies claim Botulinum toxin to be highly effective in reducing blepharospasms with ambiguous results in dry eye relief.<sup>15,16</sup> Botulinum toxin injection has also been recommended in treatment of blepharospasm in children older than 2 years.<sup>18</sup>

**Disorders Of The Eyelid:-**

Botulinum toxin injection into the Levator muscle may be used to induce a temporary protective ptosis in patients with Lagophthalmos for corneal protection. 2.5-5 U may be injected into the Levator muscle.<sup>19</sup> It is considered superior to Tarsorrhaphy as it is associated with less fibrosis and scarring. However, care has to be taken to note that induction of Superior rectus weakening during induction of temporary ptosis may lead to weakness of the Bell's reflex, hypotropia and corneal exposure. This in turn can neutralize the protective effect of a temporary ptosis.<sup>20</sup> A study by Sadiq et al notes that this complication occurred less frequently with transconjunctival route than with transcutaneous Botulinum toxin injection.<sup>21</sup> Botulinum toxin injections (5-10U) into the pretarsal and /preseptal orbicularis muscle may be used in the management of Congenital, Senile and Spastic types of Entropion with temporary relief to the patient<sup>22,23,24,25</sup>

**Thyroid Eye Disease:-**

A significant proportion of patients with Thyroid eye disease (TED) present with diplopia, which is managed with prisms in the acute phase and by surgery after the active phase. Chemodenervation with Botulinum toxin is another management option, which can be used in the active phase of the disease and is found to have good results in patients with less than 20 PD of deviation, reducing the deviation prior to surgery and in some cases, completely eliminating the need for surgery.<sup>26</sup> Complications include transient ptosis and transient muscle weakness. Use of Botulinum toxin in the early phase of TED may be used in patients not benefitting from prismotherapy, and it reduces the amount of surgical correction and in some cases, completely eliminates the need for surgery.<sup>27</sup>

**Epiphora:-**

Botulinum toxin injection into the palpebral part of the lacrimal gland is considered to be an alternative treatment to Conjunctivodacryorhinoplasty with tube implantation.<sup>28,29</sup> This is a less invasive procedure and requires less expertise. A transconjunctival approach is preferred. It has been suggested as a treatment modality in epiphora due to lacrimal outflow obstruction in the elderly and frail and in those in whom the lacrimal outflow apparatus has been excised (eg malignancies).<sup>30</sup> A similar treatment is also advocated for the treatment of “Crocodile tears”(Gustatory hyperlacrimation) with good results.<sup>30,31</sup> Complications include ptosis, lagophthalmos, diplopia, dry eye etc.<sup>30</sup>

**Dry Eye Disease:-**

Dry eye disease is a chronic disease which causes a number of debilitating symptoms to the patient. Different treatment modalities are based on supplementation/ replacement of tears, stimulation of tear production and retarding tear drainage.<sup>32</sup> Botulinum toxin use in dry eye disease is based on the last principle. The mechanism of action is by temporary pharmacological paralysis of the Orbicularis oculi pars lacrimalis muscle, reduced lacrimal pump action, increased tear retention and wetting of the ocular surface.<sup>33,5</sup> A dosage of 2.5-3.75 U may be used. It is considered to be a good alternative to punctal plugs and is associated with lesser incidence of complications and greater patient satisfaction and improved quality of life. However, it is considered to be a temporary therapeutic measure. Treatment was associated with improved TBUT, Lissamine green staining and OSDI scores<sup>34</sup> Some studies recommend injecting only in the lower eyelid.<sup>35</sup>

**Migraine And Chronic Ocular Pain:-**

Botulinum toxin A has been FDA approved for prophylaxis of chronic migraines.<sup>36</sup> It is postulated to inhibit neurotransmitter release from the nerve endings, both at the peripheral level and also at the level of the central terminals, inhibition of 2<sup>nd</sup> order neurons and inhibition of the headaches. A transynaptic transport model has been hypothesized<sup>37</sup>. It was found to be effective in prophylaxis of chronic headaches, but not so beneficial in episodic migraines and tension headaches.<sup>36,38</sup> The above treatment could reduce the dependence on oral medications and combination treatments in chronic migraine patients.<sup>39</sup> It may also be used for conditions with chronic eye pain like myositis and other spasmodic conditions with good results.<sup>40</sup>

**Other Uses:-**

Botulinum toxin injections have been used for the management of facial, forehead and periorbital wrinkles and also for treating lower lid wrinkling and causing eye widening.<sup>1,41</sup> It may also be used to improve the facial asymmetry in patients with Facial nerve palsy<sup>42</sup>

**Conclusions:-**

The advent of Botulinum toxin use in Ophthalmology has drastically improved the management of a number of ophthalmological conditions, especially in conditions involving the ocular muscles, lacrimal system disorders and skin disorders like eyelid wrinkles. It represents a less invasive management option which is simple, cheap and requires a lesser learning curve for the surgeon. Further studies to find newer uses of this drug and discovering other similar agents would be a highly exciting ophthalmological research challenge.

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