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"A Review on Botulinum Toxin Safety and Efficacy in Treatment of Blepharospasm and Hemifacial Spasm"

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Abstract:
Background:
Botox(serotype A)is currently available&used to treat various ophthalmological conditions.The aim of our study was to review the efficacy&safety&updates on the clinical use of botulinum toxin-A(Btx-A)in the treatment of blepharospasm(BS)/benign essential blepharospasm(BEB)&hemifacial spasm(HFS)
Materials and Methods:
A literature search using the keywords Botulinum toxin,Botulinum toxin types,Treatment of BS/BEB&HFS was performed using PUBMED,GOOGLE SCHOLAR,INDMED.We screened titles,keywords&Articles describing the use of Btx-A were selected and reviewed
Results*:*
The Btx-A is used to treat BS/BEB&HFS. For cosmesis, it can be used to relax facial muscles to reduce wrinkles.The efficacy of Btx-A in BS/BEB and HFS is almost above 90% and there was no difference in both the conditions.In our review we found that the safety of Btx-A in BS/BEB is superior to the HFS.Complications of the injection include local effects like ecchymosis,pain/infection&spillover effects like ptosis,diplopia,lagophthalmos,mid facial weakness&watering of eyes
Conclusion*:*
The clinical application of Btx-A in ophthalmology is extensive.When considering its application in clinical practice,one should be mindful of the indications,risks and benefits of the procedure.In our review we have noted that both BS/BEB&HFS were well treated with Btx-A.Relief of symptoms were similar in both the BS/BEB&HFS.Various formulations of Btx-A shown similar efficacy and safety in treatment of BS/BEB&HFS
Keywords: *BOTULINUM TOXIN, TREATMENT OF BLEPHAROSPASM/BENIGN ESSENTIAL BLEPHAROSPASM & HEMIFACIAL SPASM*

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I. Introduction:

BENIGN ESSENTIAL BLEPHAROSPASM/BLEPHAROSPASM:

Benign essential blepharospasm/blepharospasm is considered an adult-onset focal dystonia of the seventh cranial nerve [27]. The disease is characterized by involuntary lid closure secondary to hyperkinetic movements of the orbicularis oculi and other periorbital muscles [28]. Frequent involuntary lid closure may render patients functionally blind, impairing quality of life [29]. It is almost exclusively binocular, although there are a few case reports of monocular disease that eventually become bilateral within months [30]. A primary and secondary form of the disease exists. Primary disease is the most commonly encountered in clinical practice. It is generally sporadic, with only rare familial or hereditary forms reported [31]. BEB is a rare disease with prevalence ranging from 20 to 133 cases per million population, primarily affecting females between 50 and 70 years old [32]. There are no clear data on ethnic predilection; however, some sources report higher incidences in Caucasians [33]. Secondary disease accounts for less than 10% of all cases and is encountered after focal insults of the brainstem, thalamus, basal ganglia, cerebellum, or even cortical areas. It has also been reported in Parkinson disease, tardive dyskinesia, Bell's palsy, ocular myasthenia gravis, or other diseases leading to corneal irritation [1,5,18,29,30,31,32,33].

Blepharospasm has a reported prevalence of 1.3 to 13 in apopulation of 100,000.The mean age of onset is the fifth to sixth decade. Blepharospasm affects women more often than men in a ratio of 2.8:1.2 The pathophysiology of blepharospasm involves impairment of central sensorimotor integration and loss of

inhibition.The diagnosis of blepharospasm is based on clinical recognition.There are a limited number of double-blind, placebo-controlled studies on BoNT efficacy for blepharospasm.More than 90% of patients with blepharospasm improve with injection[1,17,18,23,31].

The pathogenesis of BEB is still unclear. Animal models suggest a contribution of both corneal irritation and basal ganglia dysfunction leading to loss of supranuclear control of the blink reflex. More recently, imaging studies have identified microstructural lesions in the cerebellum that correlated with disease severity.

BEB is a clinical diagnosis and is important to distinguish from other conditions of involuntary eyelid closure such as tics, HFS, facial chorea, eyelid-opening apraxia, frequent blinking, or lid ptosis. The presence of stereotypic bilateral synchronous orbicularis oculi spasms and either a sensory trick or increased blinking are necessary to make the diagnosis[1,5,18,29,30]

HEMIFCIAL SPASM (HS):

Hemifacial spasm is an involuntary synchronous tonic and/or clonic contraction of facial muscles, caused by dysfunction of the ipsilateral facial nerve [1, 2]. HFS may be confused with other facial movement disorders such as benign essential blepharospasm, Meige syndrome, tardive dyskinesia, oromandibular dystonia, facial tic, facial myokymia or myorhythmia, facial myoclonus, facial nerve aberrant regeneration, or psychogenic facial spasm. The diagnosis remains clinical and is critical to targeting appropriate therapy.

It has a female predominance, with peak onset in the 40–60-year age range, affecting approximately 10 per 100,000 people. Bilateral hemifacial spasm (HFS) is exceedingly rare; an alternative diagnosis should be sought in cases with bilateral movements [3]. The disease is almost exclusively sporadic, yet a rare autosomal dominant familial form has been described [4, 5].

Primary HFS is caused by aberrant or ectatic vessel compression of the facial nerve [6, 7]. High-resolution 3-dimension (3-D) magnetic resonance imaging (MRI) identified a single vessel compressing the facial nerve in 52% of cases, and multiple vessel compression in 48% of cases. The anterior inferior cerebellar artery (AICA, 50%) and posterior inferior cerebellar artery (PICA, 45%) were the most common compressing single vessels, while the combinations of the vertebral, AICA, and PICA accounted for the multiple compression group [8]. Secondary HFS results from an insult to the facial nerve along its course from the cerebellopontine angle to the parotid glands, most commonly between the internal auditory canal and the stylomastoid foramen; causes include trauma, tumor, infection, vascular anomalies, or an idiopathic lower motor neuron seventh [6, 9, 10]. Vascular compression most often affects the facial nerve at the brainstem root exit zone [7, 11]. Atherosclerotic disease, hypertension, genetics, facial nerve hyperexcitability, and low posterior cranial fossa volumes have been implicated in the pathogenesis of HFS [11–16].

The two commonly accepted hypotheses connecting nerve compression and subsequent spasms (the peripheral/ephaptic transmission theory and the central/hyper-excitable nucleus theory) do not fully explain the immediate symptomatic and electrophysiologic improvement following microvascular decompression (MVD) [17–20]. The immediate improvement following MVD as well as symptom exacerbation by anxiety or other emotional states are best explained by a third theory, the "autonomic theory." It postulates that the facial nerve compression produces an ectopic action potential in the demyelinated fibers that later induces the spasm[21, 22]. The actual mechanism may be some combination of the three theories, with the common denominator of initial vascular compression.

HFS semiology usually involves a lower eyelid onset with subsequent spread to other periorbital, midfacial, perioral, and/or platysma muscles in a synchronous manner. Orbicularis oculi is the initial site of spasm in 90% patients [23]. Accordingly, patients may experience initial visual and psychosocial symptoms related to an episodic facial disfigurement with lid closure. In a HFS cohort, depression was more common in younger females [24]. Symptoms tend to increase with voluntary facial movements, stress, fatigue, and anxiety; unlike blepharospasm (BEB), spasms may persist during sleep. Relaxation, alcohol, exercise, and tactile stimulus to the affected region have been reported to provide symptomatic improvement. Bilateral HFS is exceedingly rare and almost always begins with unilateral contraction followed by bilateral asymmetric contraction. In about 4% of patients, HFS may coexist with trigeminal neuralgia and is referred to as "tic convulsif"; this constellation is usually due to the same offending vessel(s). Some patients report an ipsilateral low-pitched tinnitus in addition to hearing loss suggestive of concomitant cochlear nerve involvement].The natural history of HFS is typically expansion followed by stability, with rare (temporary) remission. [1,5,14,17,28,30,31]

BOTOX:

Botulinum toxin, also called "miracle poison," is one of the most poisonous biological substances known.[1] It is a neurotoxin produced by the bacterium *Clostridium botulinum*, an anaerobic, grampositive, spore-forming rod commonly found on plants, in soil, water and the intestinal tracts of animals. Scott, first demonstrated the effectiveness of botulinum toxin type A for the management of strabismus in humans.

Subsequently, botulinum toxin was approved for the treatment of numerous disorders of spasticiy[1] and a host of other conditions. Currently it is used in almost every subspecialty of medicine. In 2002, the FDA approved the use of Botox (Botulinum toxin-A) for the cosmetic purpose of temporarily reducing glabeller forehead frown lines.[3,21,23]

Biochemical aspects

C. botulinum elaborates eight antigenically distinguishable exotoxins (A, B, C , C , D, E, F and G). Type A is the most potent toxin, followed by types B and F toxin. Types A, B and E are commonly associated with systemic botulism in humans.[3] All botulinum neurotoxins are produced as relatively inactive, single polypeptide chains with a molecular mass of about 150 kDa with a high degree of amino acid sequence homology among the toxin types. The polypeptide chain consists of a heavy (H) chain and a light (L) chain of roughly 100 and 50 kDa respectively, linked by a disulfide bond.[4] The botulinum toxin neurotoxin complex is also associated with various other nontoxic proteins, which may also have hemagglutinating properties.[3,21,23]

How botulinum toxin works:

All the serotypes interfere with neural transmission by blocking the release of acetylcholine, which is the principal neurotransmitter at the neuromuscular junction. Intramuscular administration of botulinum toxin acts at the neuromuscular junction to cause muscle paralysis by inhibiting the release of acetylcholine from presynaptic motor neurons.Botulinum toxins act at four different sites in the body: The neuromuscular junction, autonomic ganglia, postganglionic parasympathetic nerve endings and postganglionic sympathetic nerve endings that release acetylcholine.The heavy (H) chain of the toxin binds selectively and irreversibly to high affinity receptors at the presynaptic surface of cholinergic neurones, and the toxin-receptor complex is taken up into the cell by endocytosis. The disulphide bond between the two chains is cleaved and the toxin escapes into the cytoplasm. The light (L) chain interact with different proteins (synaptosomal associated protein (SNAP) 25, vesicle associated membrane protein and syntaxin) in the nerve terminals to prevent fusion of acetylcholine vesicles with the cell membrane.The peak of the paralytic effect occurs four to seven days after injection. Doses of all commercially available botulinum toxins are expressed in terms of units of biologic activity. One unit of botulinum toxin corresponds to the calculated median intraperitoneal lethal dose (LD) in female Swiss-Webster mice.The affected nerve terminals do not degenerate, but the blockage of neurotransmitter release is irreversible. Function can be recovered by the sprouting of nerve terminals and formation of new synaptic contacts; this usually takes two to three months.

Botulinum toxin induces weakness of striated muscles by inhibiting transmission of alpha motor neurones at the neuromuscular junction. This has led to its use in conditions with muscular overactivity, such as dystonia. Transmission is also inhibited at gamma neurones in muscle spindles, which may alter reflex overactivity.The toxin also inhibits release of acetylcholine in all parasympathetic and cholinergic postganglionic sympathetic neurons. This has generated interest in its use as a treatment for overactive smooth muscles (for example, in achalasia) or abnormal activity of glands (for example, hyperhidrosis)[3,21,23]

The toxin requires 24-72 hours to take effect, reflecting the time necessary to disrupt the synaptosomal process. In very rare circumstances, some individuals may require as many as five days for the full effect to be observed. Peaking at about 10 days, the effect of botulinum toxin lasts nearly 8-12 weeks. The best availabletreatment is repeated botulinum toxin (BTX) injections.BTX, one of the most poisonous biological substances known, is a neurotoxin produced bythe bacterium *Clostridium botulinum*. *C. botulinum* an anaerobic Grampositivesporulatingorganism(abaneh) elaborates eight antigenically distinguishable exotoxins (A, B, C , C , D, E, F and G). All serotypes interfere with neural transmission by blockingthe release of acetylcholine, the principal neurotransmitter at the neuromuscular junction, causingmuscle paralysis. The weakness induced by injection with botulinum toxin A usually lasts about threemonths[3].Scott and associates initiated the therapeutic use of BTX and showed theweakening effect of BTX on monkey extraocular muscles in 1973.He later studied the effect inhumans and published the first reports of its clinical use in treating strabismus.Since 1989, BTX has been shown to be an effective therapy for more than 100 clinical disorders characterized by involuntary muscle activity, excessive muscle tone, pain syndromes and hypersecretoryconditions,and the drug has been the mainstay of treatment in BEB and HFS for overtwo decades[3,21,23,3]

Botulinum toxin preparations can achieve organ-selective temporary chemodenervation when injected near the nerve that controls the target organ.This can provide patients with a therapeutic modality that may improve both their medical condition and quality of life[4] The therapeutic benefits derived from a local injection of a botulinum toxin preparation are based on site-specific delivery (e. g., intramuscular, subcutaneous) and the fact that these compounds have a high affinity foruptake by cholinergic neurons. This results in a temporary chemodenervation and the loss or reduction of neuronal activity at the target organ (e. g., muscle,glands) with minimal risk of systemic adverse effects, when used at the appropriate dose[4,23,32,33]

MECHANISM OF ACTION OF BOTOX:

The mechanism of action of the seven botulinum neurotoxin serotypes (A, B, C1, D, E, F, and G) has been reviewed in other publications.[4]. Although serotypes C1 and E have been used in a limited number of volunteers and patients,their role astherapeutic agents requires further clinical studies. To date, the vast majority of commercial development of botulinum toxin for clinical use has been based on BTX-A. However, studies indicate that botulinum neurotoxin serotypes B (BTX-B) and F (BTX-F) may be useful for the treatment of cervical dystonia or blepharospasm.Clinical studies have found that BTX-A is more potent (less total number of units administered per patient per session) than BTX-B [7, 8, 13] and has a longer duration of action than either BTX-B, as indicated by electromyography (EMG) results only [13], or BTX-F as indicated by clinical response [6, 12, 14].

Serotype A is the only commercially available form of botulinum toxin for clinical use, although experience is emerging with development of other serotypes: B, C, and F preparations.[12] Two preparations of botulinum toxin A exist: Dysport and BotoxBotox is a sterilelyophilized form of botulinum toxin type A.(3)Botulinum toxins now play a very significant role in the management of a wide variety of medical conditions, especially strabismus and focal dystonias, hemifacial spasm, and various spasticmovement disorders, headaches, hypersalivation, hyperhidrosis, and some chronic conditions thatrespond only partially to medical treatment. The list of possible new indications is rapidly expanding.The cosmetological applications include correction of lines, creases and wrinkling all over the face,chin, neck, and chest to dermatological applications such as hyperhidrosis. Injections with botulinumtoxin are generally well tolerated and side effects are few. A precise knowledge and understanding ofthe functional anatomy of the mimetic muscles is absolutely necessary to correctly use botulinum toxins in clinical practice[3]

SAFETY AND ANTIGENECITY:

Botulinum toxin therapy has been demonstrated to be safe in a variety of conditions (BTX-A only, BTX-B has only been studied in cervical dystonia) when administered appropriately. The most common adverse effects are either excessive weakness of the treated muscle or the local diffusion of the neurotoxin from the injectionsite causing unwanted weakness in adjacent muscles. For example, the following can occur: hand weakness when excess BTX-A diffuses into the muscles from the subcutaneous locations used to treat palmar hyperhidrosis; ptosis when the levator muscle is affected during treatment of blepharospasm, brow furrows, or headaches; and dysphagia (BTX-A or BTX-B) in patients treated for cervical dystonia [36, 50, 51]. All of these muscle-weakness adverse effects with BTX-A are generally mild and of limited duration. The escape of minute quantities of BTX-A from the treated cervical muscles has been reported [37, 38]. These events were measured by a single fiber electromyographic technique and recorded as an "EMG jitter" in a distal limb. There was no clinically significant weakness associated with these observations. Similar human EMG jitter studies remain to be conducted with the BTX-B preparation. The preclinical efficacy and safety of the two BTX-A commercial botulinum neurotoxin preparations (Botox® and Dysport®) were compared following a single intramuscular injection in mice [39]. The mouse digit abduction scoring (DAS) assay was used to assess the local muscle-weakening efficacy of these preparations.

The systemic effect was measured as the first dose to cause significant reduction of weight gain in the treated mice.Botox® was observed to have a larger safety margin than Dysport® (Table 1) when compared with Dysport® for the ratio of local efficacy (DAS score) and the first dose that caused a significant weight loss (10 mice per dose group). These results suggest that the two preparations of BTX-A possess different dose ratios for local efficacy than ratios at doses where the toxin escapes the injection site to exert a systemic effect. Thus, simple conversion of units between the two products should be avoided, especially at the higher doses. Any simple unit conversion factor does not address these differences or consider the antigenic potential of the preparations. This concept should apply to other botulinum toxin serotype preparations as well[3,4,23].

Therapy of hemifacial spasm with BTX-A:

Hemifacial spasm is clinically marked by involuntary unilateral contraction of the muscular system innervated by the facial nerve; contact of that nerve with a vessel near the brain stem is the cause. The clinical picture may vary substantially. Some patients merely present with contractions in the region of the orbicularis oculi muscle. In other patients, the entire musculature innervated by the facial nerve including the platysma may be involved. Mild progression of disease is seen in many cases. Neurogenic damage is due to vessel/nerve contact with the result of mild facial paralysis. The clinical picture apart, electroneurography of the facial nerve and electromyography of the muscle supplied by the facial nerve are helpful. The vessel/nerve contact may be demonstrated by MRI. For treatment, carbamazepine a membrane-stabilizing drug is used among others. The surgical procedure in use is vascular decompression of the facial nerve (Janetta's technique). The injection of botulinum toxin has meanwhile been recognized as the treatment of choice. Nearly all of the muscles affected can be injected.We should watch out for functional impairment though, seen in the angles of the mouth for

instance. Small doses are generally sufficient, in quantities frequently lower than those administered for blepharospasm.
We refer to the pertinent literature for the amounts injected and the sites of injection[18,23].

Therapy of blepharospasm with BTX-A:

Blepharospasm is a form of dystonia involving the orbicularis oculi muscle, which may also affect adjacent muscles innervated by th facial nerve.Major incidence has been observed in mean and advanced adult age. Involuntary contractions commonly occur on both sides and synchronously but differing in prominence.We distinguish the clonic and tonic type from the lid opening inhibition type.Meige's syndrome with involuntary contraction of additional muscles innervated by the facial nerve has to be ruled out. Contrary to hemifacial spasm, these contractions are not synchronous. Because of the poor response to systemic medication (e. g. anticholinergics, atypical neuroleptic agents), the injection with BtA has become the treatment of choice. The injection scheme is a simple one,with differing injection points selected by different users. Injection close to the levator palpebrae muscle should be avoided as this will inevitably lead to ptosis[18,23].

II. Objectives:

To review the clinical efficacy & safety of Botulinum toxin-A for thetreatment of blepharospasm(benign essential blepharospasm) & hemifacial spasm

III. Methods:

A literature search using the keywords Botulinum toxin,Botulinum toxin types, Treatment of BS/BEB&HFS was performed using PUBMED,GOOGLE SCHOLAR,INDMED. We screened titles,keywords&Articles describing the use of Btx-A were selected and reviewed. Some articles were added based upon the references of the initial articles. We screened titles, keywords and abstracts of the citations downloaded from the electronic searches and obtained full copies of reports of potentially suitable trials for further assessment.

IV. RESULTS:

References	Study design	Botox a	Disease	Number of BS& HFS patients	Efficacy& safety outcome	Results/remarks
Karp BI, Alter K.[1]	Doule blind control study	Btx-A	blepharospasm, orofacial/oro mandibular dystonia, and hemifacial spasm		Found to be safe and effective	BS: More than 90% of patients with BS improve with injection HFS:76 to 100% of patients have over 75% improvement Adverse events: BS: in 3 to 25% HFS: 20% of injection sessions It offers a safe and effective treatment for a disorder without other adequate therapeutic options
Ababneh OH, Cetinkaya A and Kulwin DR[2]	Retrospective	Btx-A	blepharospasm and hemifacial spasm	BS:21 HFS: 11	Found to be safe and effective	Success rates in: BEB:93.8% HFS:96.9% The most common adverse events were ptosis, lagophthalmos and dry eye BEB:11.5% HFS:3.8%
Green KE,Rastall D &Eggenberger E[5]	Retrospective	Btx-A	Blepharospasm/Hemifacial spasm		Found to be safe and effective	Success rate: BEB:89% HFS:85% of HFS BS therapy employs botulinum toxin with corneal lubrication, and surgical myectomy in refractory cases; HFS may be effectively treated with botulinum toxin

Ainsworth JR, Kraft SP[6]	prospective	Btx-A	Essential Blepharospasm and Hemifacial Spasm	BEB:20 HFS: 12	Statistical analysis showed no significant changes in mean duration of relief within each group (*P* = 0.65 for essential blepharospasm, 0.36 for hemifacial spasm). There was a trend to slow decline in the interval of relief, especially in patients with an initial duration of effect greater than 150 days.	Success rate: BS & HFS: 98.9% Adverse effects: BEB: 35%: HFS:20% No relation was found between duration of relief and age or sex of patient or grade and duration of disease before initial treatment
Borodic G et-all[7]	double-blind study,controlled	Btx-A	Aberrant facial nerve regeneration	30		
Brin MF et-AL[8]		Lyophylized botox	Focal Dystonia and Hemifacial Spasm	BS:46	Found to be safe and effective	Success rate: BS: 69% 2 patients developed antibodies against the toxin
ÇakmurR,OzturkV,Uzunel F, Donmez B, Idiman F[9]	Comparative	Botox®, Allergan)	preseptal and pretarsalinj, in blepharospasm and hemifacial spasm	BS:25 HFS:28	Found to be safe and effective	Success rate: Preseptal: BS:92%,HFS:86% Pretarsal: BS:97%,HFS:96% Adverse effects(Ptosis): Preseptal 16%&18% Pretarsal13&7%
Jochim A, MeindlT,HuberC,MantelT, ZwirnerS,CastropF,Haslinger B[10]		aboand onabotulinumtoxinA	blepharospasm and Meige's syndrome	69:onabotulinum 282:abobotulinum	Found to be safe and effective	Improvement in BS with Onabotulinum:86% Abobotulinum:92%
Gürsoy AE, Ugurad I, Babacan-Yıldız G, Kolukısa M, Çelebi A[11]			hemifacial spasm and blepharospasm	BS:26 HFS:53		At baseline, physical health, psychological well-being, and satisfaction with the environment domain scores of WHOQOL-BREF TR, HDRS and HAS scores were not significantly different in two patient groups. Social relationship domain score was found significantly higher in HFS group compared with BLS group. BtxA therapy resulted in a significant improvement of clinical symptom severity, of all domain scores of WHOQOLBREF TR and of depression and anxiety scores in both HFS and BSP groups. Conclusions: This study demonstrates significant benefit of Botulinum toxin therapy on quality of life, depression and anxiety in patients with BSP and HFS.
Carruthers J and Stubbs[12]		Btx-A	Benign Essential Blepharospasm, Hemifacial Spasm and Age-Related Lower Eyelid Entropion	BEB:47 HFS:11	Found to be safe and effective	The treatment was Effective Side effects:7.8% overall
Czyz CN, Burns JA, Petrie TP, Watkins JR, Cahill KV, Foster JA[13]	retrospective cohort	Btx-A	benign essential blepharospasm, hemifacial spasm, and Meige syndrome	BEB :26 HFS:7	Found to be safe and effective	BEB&HFS treatment was successfull 20% incidence of minor adverse events Botox treatment for BEB, hemifacial spasm, and Meige syndrome is clinically successful, with a low incidence of adverse events, even when treatment durations extend to 20-plus years for individuals who tolerated treatment for 15 years.
Dutton JJ, Buckley EG[14]		Btx-A	Essential blepharospasm Hemifacial spasm Meige's	BS:145 HFS:60	Found to be safe effective	sustained improvement in the severity of their spasms in BS&HFS is 96.9% In total 22.6% adverse effects seen There was good efficacy and safety noted There was no significant correlation in degree of spasm reduction with increasing dose of

			syndrome			toxin from 12.5 to 75 U per eye.
Frueh BR, Nelson CC, Kapustiak JF, Musch DC[15]		Btx-A	Blepharospasm	BS:26	Found to be safe and effective	87% relief symptoms in BS 13% insufficient relief Since the inferior oblique muscle is closest to the medial two thirds of the lower eyelid, avoiding that site during toxin injection will likely result in little or no inferior oblique muscle paresis, while maintaining a high likelihood of relief of spasm.
Girlanda P, Quartarone A, Sinicropi S, Nicolosi C, Messina C[16]		Btx-A	Blepharospasm single fiber electromyography and blink reflex study	BS:6	It was effective and safe	All 6 patients experienced an improvement of their BS without complaints related to local side effects findings in BS are consistent with an effect of botulinum toxin merely in the motor end-plates. This effect is present bilaterally also for unilateral injection probably because of toxin spreading
Kocabeyoglu S, Sekeroglu HT, Mocan MC, Muz E, Irkec M, Sanac AS.[19]	prospective study	Botx-A	ocular surface changes in BS	BS:13	It was effective and safe	Botulinum toxin A injection appears to have a positive but temporary effect on ocular surface parameters in patients with blepharospasm. 8 patients (61%), blepharospasm recurred within the 6-month period and necessitated Botox reinjection after the final visit. None of the subjects experienced Botox injection–related adverse effects.
Yoon JS, Kim JC, Lee SY[20]	Double-Blind, Randomized, Comparative In essential bs	Meditoxin and botox	Blepharospasm	BS:60	Meditoxin® and Botox® were comparable in efficacy and safety in the treatment of essential blepharospasm	Improvement in BS was noted in 90.3% of the Meditoxin® group and 86.2% of the Botox® group.
Wabbels B, Reichel G, Fulford-Smith A,[22]	double-blind, randomised, parallel-group comparison	study of two BoNTA PRODUCTS	Belpharospasm	Botx:32 Xeomin :33	No difference in effectiveness and safety between the products	Both BoNTA products were well tolerated and the numbers of subjects in each group who reported at least one adverse event were not significantly different (n = 26 subjects BOTOX_ vs. Xeomin_; P = 0.752) No significant differences between products were noted in PGA and adverse events at the doses used in this study.
Ho RW, Fang PC, Chao TL, Chien CC, Kuo MT[24].	prospective case series,	Btx-A	changes in the tear film lipid layer thickness (LLT) and aqueous tear production after botulinum neurotoxin A (BoNT) injection in patients with (BEB) and (HFS).	BS:11 HFS:6	Effects on the LLT increased after Botx-A	LLT, a decisive factor for tear film stability, significantly increases at 1 month after BoNT injection for BEB and HFS overall post-treatment complication rate was 23.5% A decrease in BSDI and an increase in the snap-back time may contribute to the increase in LLT; this mechanism is probably responsible for the relief from dryness after BoNT injection in patients with facial movement disorders.
Park DI, Shin HM, Lee SY, Lew H[25]	prospective study	Btx-A	tear production, distribution and drainage in the essential blepharospas	BS:23	It was effective and safe as Tear production was increased after Botx-A	Botulinum neurotoxin A treatment relieved blepharospasm in all patients Tear film stability and TMH increased, but tear drainage velocity was not affected by BoNT-A treatment Overall Tc-99m 50% clearance time in interpalpebral fissure significantly

			m			increased, and tear storage from mild lateral lower eyelid laxity increased after BoNT-A injection. Botulinum neurotoxin A injection was also effective for combined dry eye symptom in the BEB patients
MacAndie K, Kemp E[26]	cross-sectional	Btx-A	Impact on quality of life of Btx-A	BS:44	It was found effective and safe	81.8% are having total benefits significant quality of life benefit from Botulinum toxin therapy for BEB and justifies continued treatment
Kollewe K, Mohammadi B, Köhler S, Pickenbrock H, Dengler R, Dressler D[27]	retrospective non-interventional design	Btx-A	Long term treatment in BS	BS:288	Found to be Effective and safe	It was stable in 90 % of the patients Adverse effect frequency was 3.0 % OVERALL Btx-A therapy is a safe and effective treatment for BS
Jankovic J, Kenney C, Grafe S, Goertelmeyer R[28]	randomized, double-blind		Relationship Between Various Clinical Outcome Assessments in Patients with Blepharospasm	BS:300	Clinical outcome was effective	The results from the observational trial and the controlled clinical trial with Xeomin1 and Botox1 confirmed the high internal consistency of the BSDI and acceptable retest reliability on the single item level.

V. Conclusion:

The clinical application of botulinum toxin A in ophthalmology is extensive.When considering its application in clinical practice, one should be mindful of the indications, risks and benefits of the procedure. In our review we have noted that both blepharospasm and hemifacial spasm are well treated with botox injection.relief of symptoms were similar in both the blepharospasm and hemifacial spasm. Side effects like ptosis lagophthalmos and watering were more with hemifacial spasm.Various formulations of type-A botulinum toxin shown similar efficacy and safety in treatment of BS AND HFS.

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