

Therapeutic Application of Botulinum Toxin in Clinical Practice

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Abstract: Botulinum toxin, one of the most potent toxins known, is produced by *Clostridium botulinum*. It causes a temporary paralysis of muscles by inhibiting vesicular release of acetylcholine in neuromuscular junction and synaptic transmission at cholinergic nerve terminals and causes a temporary paralysis of muscles. Since the approval of botulinum toxin A by FDA for strabismus and blepharospasm in 1989 and botulinum toxin B for cervical dystonia in 2000, its therapeutic uses are expanding. To date, both the serotypes A and B have been used therapeutically. These include various dystonic movement disorders, lacrimal hypersecretion, hyperhidrosis, overactive bladder syndromes both neurogenic and idiopathic, prostatic hyperplasia, various gastrointestinal disorders, headache syndromes like migraine and various spastic disorders. Botulinum toxin does not correct the underlying pathology but only produces clinically symptomatic improvement. The duration of improvement and the percentage of improvement vary between different studies due to differences in doses used; different techniques used for injections and also the dilutions. Still more trials are required to explore newer indications of its use, to find out the exact effective doses, dilutions and techniques, so as to have a prolonged clinical improvement. Though it has a good safety profile, complications are related to chemodenervation of adjacent muscles and injection techniques. This article provides an update on different uses of botulinum toxin in medicine.

Key Words: Botulinum toxin, botox in clinical practice, botulinum toxin in medicine.

INTRODUCTION

Botulinum toxin, one of the most potent toxins known, is produced by *Clostridium botulinum*. It is associated with lethal outbreaks of food poisoning. A very small amount of toxins produces a descending paralysis with prominent bulbar symptoms and at times autonomic symptoms. It exerts its toxic effect by inhibiting synaptic transmission at cholinergic nerve terminals by preventing exocytosis of acetylcholine. Toxic effects occur mainly at the neuromuscular junction, but ganglionic nerve terminals can be affected [1].

Strains of *Clostridium botulinum* produce seven antigenically distinct neurotoxins as serotypes A to G, out of which the most stable and most potent exotoxin is botulinum toxin A (Botox-A). All seven serotypes contain a unique zinc dependent endo-peptidase the light chain, which is bound to a heavy chain and joined by a disulfide bond, in complex with hem agglutinin & nontoxic-non hem-agglutinin proteins. Different preparations have different total weights of these complexes. The total weight complex may be a factor, determining diffusion of the toxin from the site where it is injected [2]. The toxin inhibits the release of acetylcholine at terminals of cholinergic neurons at the neuromuscular junction. With the propagation of action potential there is an activation of calcium channels, which in turn cause Synaptosomal Associated Protein Receptor (SNARE) proteins to aggregate to form complexes. This causes the fusion of vesicle containing acetylcholine with the synaptic membrane and

acetylcholine is released in to neuromuscular junction. The toxin inhibits the aggregation and complex formation of SNARE proteins. The SNARE complex consists of synaptosomal associated protein (SNAP25), Synaptobrevin or vesicle Associated Membrane Protein (V Amp) and Syntaxin [3]. They bind to the presynaptic membrane by heavy chain and is internalized to the cytosol of the membrane, where the light chain is catalytic and translocated to the external surface of the synaptic vesicle, deactivates the SNARE proteins that are needed for docking and fusion of the synaptic vesicle with the terminal membrane [4]. Botulinum toxin B, D, F & G cleave specifically at single but different peptide bonds Vamp / synaptobrevin, a membrane protein of synaptic vesicle. Botulinum toxin A, C, E cleaves SNAP 25 at different sites, where as Botulinum toxin C also cleaves Syntaxin [5]. They all interfere with neuromuscular transmission by blocking the release of acetylcholine and cause muscular weakness. Denervation of neuromuscular junction does not cause permanent damage to nerve terminals and is reversible and the functions can be recovered by axonal sprouting and formation of new synaptic contacts, which usually takes two to three months [6]. The mechanism of recovery is not known. A reduction in acetylcholine esterase levels lead to receptor sensitivity and there is up regulation of extrajunctional acetylcholine receptors along with increased lysosomal and endolytic activity, which may contribute to recovery [7]. In 1989, FDA approved botulinum toxin A (Botox) as a therapeutic agent in patients with strabismus, blepharospasm and other facial nerve disorders [8]. In 2000, FDA approved botulinum toxin A and botulinum toxin B (Myobloc) as the treatment for cervical dystonia and Botox cosmetics for the treatment of glabellar lines [6].

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Botulinum toxin has to be injected to the affected muscles or glands. The doses vary according to the condition and also the size of affected muscles; the large muscles require high doses. Affected muscles can be identified by muscular hypertrophy, stiffness and visible abnormal activity. EMG is useful to identify the affected muscle. In addition, an application in pain management has been indicated by the ability of botulinum toxin to inhibit neuropeptide release from nociceptors, thereby blocking central and peripheral pain sensitization process [9].

The effect of botulinum toxin lasts only for about 3 months after which the patient will need further injection. Patients will experience relief of symptoms after each injection, followed by gradual resistance to further injection due to the development of neutralizing or blocking antibodies [10]. The mechanism of this resistance is unknown. However, immuno resistant patients account for fewer than half of patients with poor outcomes, which are likely due to technical aspects of injection, including selection of muscles injected, dose, dose limiting side effects like localized weakness or incorrect diagnosis. Advances in the purification of botulinum toxin have further reduced the risk of an immunological side effect. This resistance can be detected by mouse protection assay or clinically by unilateral brow injection which fails to produce paralysis of corrugator or procerus muscle [6]. The presence of blocking antibodies implies that the patient will not respond to the same serotype, but may respond to an alternate type; however there may be immuno resistance due to cross reactivity.

The development of resistance can be minimized by giving the lowest effective dose & long intervals between the injections. In the current Botox preparation the risk of development of blocking antibodies is nil in comparison to 9.5% of risk in original botulinum toxin A and the risk of antibody formation is low after current botulinum toxin type A treatment is related to the lower protein load [11]. Serotype B is the focus of several studies in patients resistant to conventional Botox A (botulinum toxin A). One indication in which resistance to Botox A is described is cervical dystonia, where treatment with Botox B is effective. But those responding to botulinum toxin A have a marginally longer duration of effect in comparison to botulinum toxin B [12].

Botox F is beneficial in patients who are resistant to Botox A. Better results are possible with higher doses of botulinum toxin F but the duration of benefit is still shorter than with botulinum toxin A, seemingly due to a shorter duration of neuromuscular junction blockade [13].

THERAPEUTIC APPLICATIONS

Since the introduction of botulinum toxin in clinical practice, its use has been expanding over the years. Botulinum toxin injection results in relief of symptoms, but it does not correct the underlying pathology. Botulinum toxin injection is found to be effective in various disorders of neurological, ophthalmic, gastrointestinal, urological, headache and dermatological conditions.

Strabismus

This is characterized by lack of ocular parallelism and is associated with over contractile state of ocular muscles. In-

jection of botulinum toxin (Botox) to the over contractile muscle causes weakness of the over active muscle and corrects strabismus. It reduces ocular deviation by 50-80% [14], making it an alternative option to surgery. Complications like transient ptosis, and sub conjunctival hemorrhage may occur.

Elevated Intraocular Pressure from Restrictive Myopathy

Patients of thyroid ophthalmopathy having restrictive myopathy may have elevated intraocular pressure in up gaze, which is difficult to manage medically and may require orbital decompression. In a small study of 8 patients it is seen that botulinum toxin injection to inferior rectus muscle causes reduction in intraocular pressure [15] which may be due to a decreased tone in extra ocular muscle and possibly due to a reduced orbital volume.

Chronic Dry Eyes

Injection of botulinum toxin to medial portion of the orbicularis oris muscle of lower eye lid or both lids has been found to be effective in decreasing lacrimal drainage, suggesting a new way to treat dry eye conditions. It is reported in a study that there is a subjective improvement in dry eye symptoms in 70% of patients [16].

Post Peripheral Facial Nerve Synkinesis

After facial nerve paralysis axonal regeneration leads to hyperactivity of the previously paralyzed muscles. Abnormal axonal branching leads to synkinetic movements characterized by involuntary contraction of muscles innervated by other branches. It is seen that a single injection of botulinum toxin is highly effective in reducing the synkinetic movements for 3-9 months [17, 18].

Hemi Facial Spasm

Hemifacial spasm is a dystonic movement of lower facial muscles. After local injection of botulinum toxin injection (Botox); it is seen that about 95% of patients had marked to moderate improvement [19].

Cervical Dystonia

This is an involuntary posture or movement of head and neck.

Spasmodic torticollis is the most common abnormal head posture. Many patients also demonstrate complex head movements. Both botulinum toxin type A & B are approved by FDA for the treatment of cervical dystonia. The toxin is injected directly into the muscles, most commonly the ipsilateral splenius capitis, scleoneus, trapizius, levator scapulae, deep paraspinal muscle, and contra-lateral sternocleidomastoid muscle. The long term safety and efficacy of botulinum toxin A in cervical dystonia is approximately 60% in patients treated over more than 10 years [20]. It is seen that chronic treatment with botulinum toxin in patients with cervical dystonia is not associated with any decline in benefit. The efficacy may improve slightly with repeated treatment [21]. The side effects like dysphagia, dysarthria, weakness and dry mouth are less in cases of botulinum toxin type A in comparison to botulinum toxin B [12].

Oromandibular Dystonia

In this condition there is involuntary opening and closing of jaw. Injections are given into masseter, temporalis and internal pterygoids for jaw closing, and digastric's and external pterygoids for jaw opening. Symptoms are reduced in 73% of patients [22]. Except for transient focal weakness, there are very few complications or systemic effects attributed to the injection. Early treatment seems to improve the success rate.

Laryngeal Dystonia

In this type of dystonia there is either a strangled voice or a breathy whisper voice. Botulinum toxins in low doses in to laryngeal muscles produce improvement in speech and are now the treatment of choice in this disorder [23]. Treatment with Botox results in normal or near normal voice in patients with adductor type dystonia and have considerable benefit in abductor type i.e. breathy, whispery voice [24]. A unilateral or bilateral EMG guided approach or indirect laryngoscopy without EMG has been used to inject the toxin to thyroarytenoid muscle. Adverse effects like hypophonia, hoarseness, dysphasia and stridor may occur but are temporary [6]. However, there is an improvement in the quality of life. In adults with disabling stuttering, botulinum toxin injection produces less consistent results.

Writer's Cramp

Injection of Botulinum toxin has been found to provide relief for writer's cramp. Pain is generally improved more than motor function. Botulinum toxin type A injections are effective in relieving symptoms in selected cases of writer's cramp, particularly in those with pronation / flexion pattern of dystonia. The writing speed improves both subjectively & objectively [25]. There is some weakness associated with improvement. The relief is only symptomatic and it does not reverse the associated dysfunction of primary motor and premotor cortex [26]. It is seen that 36% of patients continued to have relief when followed up for a mean period of 12 months [27].

Tics

Botulinum toxin also gives satisfactory results in tics, myoclonic jerks, and stuttering, [28], including motor tics associated with Tourette syndrome [29].

Spasticity

Botulinum toxin has been found to be effective in various spastic disorders. It has been found to relieve spasticity in cerebral palsy, strokes, multiple sclerosis, and traumatic spinal cord injury. Injections are said to relieve the muscle spasm, allowing the caregiver to wash, dress the patient & also relieve pain. It is seen that local injection of botulinum toxin can relieve disability of wrist and fingers after a stroke in 62% of subjects and the benefit lasted for 12 weeks [30]. Injection of botulinum toxin to patients of multiple sclerosis having spasticity of hip adductors also relieves muscle spasm and functional improvement. In Parkinsonism local injection of botulinum toxin also improves spasticity and rigidity. There is a clear temporal relationship between Botulinum toxins A injection in to calf muscles of parkinsonism patients

and improvement in freezing of gait. In a study it is seen that 40% reported marked improvement in freezing of gait and the mean duration of improvement lasted for 6 weeks [31]. Botulinum toxin injection has also been found to be safe and effective in the treatment of spastic toes [32]. Use of intramuscular botulinum toxin type A as an adjunct to physiotherapy and orthoses helps to reduce spasticity and improve functional mobility in children with spastic diplegia or hemiplegia in cerebral palsy [33], there by improvement of gait occurs in children with cerebral palsy.

Tremor

Benign essential tremor is the most common cause of clinically symptomatic tremor. It is due to oscillatory contraction of reciprocally innervated agonist and antagonist muscles. Botulinum toxin has been used for treatment of essential tremor with significant improvement in postural tremor of hand [34]. Treatment with botulinum toxin is worth considering in these conditions, but the main disadvantage is a dose dependant hand weakness.

Focal Hyperhidrosis

In this condition there is excessive sweating of the palms, feet and axilla. Botulinum toxin injection considerably reduces the secretion of sweat. In an open study of higher dose of botulinum toxin A in axillary hyperhidrosis [35], it was seen that intracutaneous high dose of botulinum toxin is capable of prolonging the anhydrotic effect in most patients. The duration of effect lasted for more than 19 months. The relapse rate was reduced after 12 months and there was no evidence of induction of neutralizing antibodies, confirming the safety of high dose of treatment. In randomized study [36], botulinum toxin B is also found to be effective in axillary hyperhidrosis, but the duration of effect was 2 - 8 months with a mean of 5 months. In a randomized study of 24 patients with severe palmar hyperhidrosis, it was seen that there was decreased sweating in patients with primary hyperhidrosis for at least 2 months in all the patients, and 6 months in most patients [37]. Botulinum toxin has turned out to be a simple and highly effective treatment option for pathological lacrimation and also in gustatory sweating [38]. Sialorrhea associated with amyotrophic lateral sclerosis, has been successfully treated with botulinum toxin in selected patients [39]. It is seen that anatomically guided injection of botulinum toxin B into the parotid and submandibular glands appears to improve sialorrhea effectively without compromising dysphagia in patients with Parkinson's disease [40].

Urinary Bladder Dysfunction

Injection of botulinum toxin is primarily used in detrusor sphincter dysynergia, frequently seen in traumatic spinal cord injury or in multiple sclerosis. In this condition there is insufficient relaxation and uncoordinated contraction of vesicular sphincter during micturition, causing complications like residual urine and ureteric reflux ultimately leading to renal damage. The rationale for using botulinum toxin is to weaken both the external and internal sphincter. Success rate of 58-88% has been reported when injections are given under urethroscopy or by EMG guidance [41]. Botulinum toxin has been found to be effective in voiding dysfunction from prostatitis [42]. Studies in patients with obstructive prostate

either hyper plastic or not, have used botulinum toxin with varying doses, dilutions and techniques and found improvement in prostatic volume, urinary flow rate and in residual urine and improvement in the quality of life [43, 44]. In addition some patients were able to void spontaneously. Injection of botulinum toxin to the external urethral sphincter seems to have a beneficial effect on chronic prostatic pain, presumably by reducing the hyper tonicity and hyperactivity of the external urethral sphincter [45]. Botulinum toxin has been found to be an effective therapy in overactive bladder both neurogenic and in idiopathic detrusor over activity. In a study of 24 patients [46] of neurogenic and idiopathic detrusor over activity, it is seen that improvement in urgency occurred first followed by incontinence and the improvement persisted up to 4 weeks. Botulinum toxin injection is effective in patients having spinal cord lesion with neurogenic detrusor over activity, even in patients with low bladder compliance. The patient may require repeat injection after 16 weeks to remain continent [47]. Botulinum toxin has been found to be effective in painful bladder, which is characterized by bladder pain that increases with bladder filling accompanied by increased day time frequency, nocturia and urgency in the absence of urinary tract infection or obvious underlying pathology. Three pilot studies using botulinum toxin in this condition with varying doses, and techniques, reported that the response rate of 20-85% and the duration of effect lasting between 1-8 months [48-50]. In a prospective study of effect of botulinum toxin A in painful bladder syndrome, at 1 year follow up, it was seen that the beneficial effect lasted at 3 months in 86% and 30% at 5 months. There was a significant decrease in pain, accompanied by increase in maximum cystometric capacity and in day time and night time urinary frequency, but after 1 year pain had recurred in all, requiring repeat injection [51]. However, this requires confirmation by a randomized placebo controlled study.

Gastrointestinal Disorders

Botulinum toxin injection appears to be safe and effective in dysphagia due to achalasia, esophageal spasm, spasm of sphincter of oddi, anal fissure and anismus. It may be a therapeutic option in elderly patients with achalasia unsuitable for surgery or pneumatic dilatation [52]. This treatment is most effective in elderly as symptomatic relief can last up to one to two years with a single injection [53]. In a study of patients with diabetic gastro paresis, botulinum toxin injection to the pylorus was found to relieve symptoms of gastro paresis [54]. In a review of the use of botulinum toxin in a large number of patients with gastro paresis it was found that 43% had a response to botulinum toxin treatment that lasted approximately up to 5 months, male gender was associated with a response and presence of vomiting as a major symptom predicted no response to botulinum toxin injection [55]. In a meta analysis of three randomized control trials, it is seen that botulinum toxin is as effective as glyceryl trinitrate for the management of chronic anal fissure and is associated with a lower complication rate. Botulinum toxin can be recommended as first line therapy for chemical sphincterotomy in patients of chronic anal fissure [56]. However, this requires a major and multicenter randomized trial to confirm this. Injection of botulinum toxin has been found to be an effective treatment in chronic anal fissure. When compared with topical nitroglycerin, botulinum toxin is a more effective

option, which acts as an alternative to surgery in patients with chronic anal fissure [57]. Basing on the concept of gastric injection of botulinum toxin, it may reduce the gastric emptying and body weight. In a study [58] it was seen that intra gastric injection is associated with weight loss and slowing of gastric emptying. However, it needs to be studied in a large number of cases to find out the doses required and the effectiveness of this form of treatment in cases of obesity.

Chronic Low Back Pain

Injection of botulinum toxin into para - vertebral muscles in patients of chronic low back pain, causes relief of pain and improvement of function in 3 weeks and 8 weeks after treatment [59].

Botulinum toxin injection to frontotemporalis muscle reduces the EMG artifacts and helps in localizing the seizure focus and in epilepsy surgery [60].

Botulinum toxin has been found to be useful in many dermatological conditions like treatment for improving glabellar frown lines. Repeated injections are necessary to maintain a long term effect [61].

Headache

Botulinum toxin has been found to be effective in tension headache and is thought to be due to its muscle relaxation /paralytic properties. The toxin is also capable of blocking the release of neurotransmitter, including substances P, from sensory nerve endings or nerve fibers innervating blood vessels near injection site [62]. Botulinum toxin injection is also useful in management of refractory headache. Various studies have shown that local injection of botulinum toxin is helpful and effective as a prophylactic treatment in migraine [63, 64]. It decreases the headache frequency, headache intensity, and headache related disability in episodic and chronic migraine patients. In a pilot study [65] to find out the possible predictors of response to botulinum toxin A in the prophylaxis of chronic daily headache. It is seen that chronic migraine patients respond better than chronic tension type of headache, unilateral headache, presence of scalp allodynia, pericranial muscle tenderness appear to be predictors of response to botulinum toxin A in chronic migraine, where as pericranial muscle tenderness may be a predictor of response in chronic type of tension type of headache. In a study [66] comparing the effectiveness of botulinum toxin versus divalproex sodium as a prophylactic management in cases of migraine, it was found that both reduced the headache frequency and the disability associated with migraine. However, botulinum toxin was better tolerated and associated with fewer side effects in comparison to divalproex sodium. Duration of illness emerged as a predictor of treatment response. It is seen that subjects with migraine with the duration of more than 30 years were significantly less likely to respond to treatment with botulinum toxin-A [67]. In a study of 8 patients with trigeminal neuralgia, it has been found that injection of botulinum toxin in to the region of zygomatic arch is effective [68].

CONCLUSION

Botulinum toxin causes temporary paralysis of muscles lasting for 3-4 months, by preventing release of acetylcho-

line at cholinergic junctions. It has an excellent safety and tolerability profile. The development of new botulinum toxin formulations has reduced the risk of neutralizing antibody formation. It is now widely used in various neurological, ophthalmological, urological, dermatological and gastrointestinal disorders, where it gives very good results. In various spastic disorders, by reducing the spasticity it helps in mobility and in physiotherapy. In cerebral palsy as an adjunct to physiotherapy and orthosis, improves the functional mobility and being able to delay or even avoid surgery until motion patterns become established. Current studies are directed towards newer clinical applications, exact dose of the injection and for better results without having any adverse events. Toxin type F is effective but have a shorter duration of effects. These may be useful in patients who develop antibodies to type A and B. So more studies are required to explore the effectiveness of other serotypes.

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ABBREVIATIONS

F.D.A	= Food Drug Administration
SNAP	= Synaptosomal Associated Protein
SNARE	= Synaptosomal Associated Protein Receptor
BOTOX	= Botulinum toxin
EMG	= Electromyography

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