Review Article

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Role of Botulinum toxin injection in neurological problems: A Short Review

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Botulinum Toxin (BoNT), a neurotoxin known for many years for its lethal nature has been in use for many cosmetic purposes for last many years. Its use in many medical problems especially chronic neurological problems has been well established in recent years. BoNT is a useful symptomatic treatment for many neurological disorders, and is emerging as one of the leading modes of treatments in the new subspecialty in neurology called "Interventional neurology." We have also been using BoNT regularly for therapeutic purposes in different neurological diseases with good success rate for last few years. We think use of BoNT-A needs to be encouraged in our country to provide relief to the patients suffering from many of the chronic disabling neurological problems.

Key Words: botulinum toxin, hemifacial spasm, spasticity

We have been hearing about the Botulinum Toxin injections for quite some time now. Commercialized cosmetic usage has been widely marketed not only globally, but also in our country in recent years. But medical use of Botulinum toxin is lagging far behind in our practice.

What is Botulinium toxin?

Botulinum Neurotoxin (BoNT) is a neurotoxic protein produced by the bacterium *Clostridium botulinum* and related species. BoNT is one of the most poisonous biological substances known and is also called `Miracle Poison`. History shows the lethal poisoning outbreaks due to consumption of botulinum contaminated food stuffs like sausages.[13] It had been once designed to be used as biological weapon during the World War II time.[32]

Botulism still is a deadly illness which can result from ingestion, enteric bacterial overgrowth, or wound infection. Food-borne botulism causes regular outbreaks with symptoms ranging from mild diplopia to muscle weakness and respiratory compromise.[36] The typical syndrome of descending weakness resulting from intramuscular injections can occur due to contamination of intravenous drugs by *Clostridium* spores are present in soil (wound botulism).[5] Infantile botulism can result from ingestion of *Clostridium* spores and is a cause of acquired hypotonia. [34]

Despite its dangerous nature, BoNT has been extensively studied and now is an established modality of treatment for various problems. Therapeutic use of Botulinum toxin was started in the late 1960s by Dr. Alan B. Scott, an ophthalmologist to correct strabismus, initially injected extraocular muscles in rhesus monkey and later in humans. Further various studies showed efficacy

of Botulinum toxin in the treatment of muscle control syndromes like blepharospasm and cervical dystonias.

In 1989, the US Food and Drug Administration (FDA) approved BoNT for treatment of blepharospasm, strabismus, and facial nerve dysfunction. In 2000, cervical dystonia became an FDA-approved indication for both serotypes A and B of botulinum neurotoxin. Current FDA-approved uses of BoNT-A also include the reduction of glabellar lines and the treatment of axillary hyperhidrosis .Today, Botulinum neurotoxin (BoNT) can be injected to achieve therapeutic benefit across a large range of clinical conditions in almost all medical subspecialities.[14] In 2002, the FDA approved the use of Botulinum toxin-A for the cosmetic purpose of temporarily reducing glabeller forehead frown lines. Since then use of BoNT-A for various cosmetic and therapeutic indications are surging up by each passing day.

Discussion

How BoNT works?

The anaerobic bacillus *Clostridium botulinum* secretes seven known serotypes of botulinum toxin, typed alphabetically A–G.[25] Botulinum neurotoxins reduce presynaptic outflow of acetylcholine, the principal neurotransmitter, at the neuromuscular junction, with a consequent diminution in muscle contraction leading to functional paralysis of the muscle injected with BoNT. 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.[16, 37] The peak of the paralytic effect occurs four to seven days after injection. The affected nerve terminals do not degenerate, but the blockage of neurotransmitter release is irreversible. Functions recover by the sprouting of nerve terminals and formation of new synaptic contacts which usually takes two to three months. Thus, the functional paralysis usually lasts for 3–4 months.[11]

There are two main commercial types: botulinum toxin type A and botulinum toxin type B. 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_{50}) in female Swiss-Webster mice. There are reported cases around 5-15% that developed secondary nonresponsiveness due to the production of neutralizing antibodies. [2, 10] Injecting more than 200 units per session and repeat or booster injections given within one month of treatment increases the risk of development of neutralizing antibodies. The lowest dose of toxin necessary to achieve the desired clinical effect should be used and reinjection within one month should be avoided to keep antibody formation as low and unlikely as possible. It is produced commercially for medical, cosmetic, and research use.
Many practitioners have chosen to administer injections under the guidance of electromyograph (EMG) monitoring. This technique involves using a 27-gauge EMG needle connected to an EMG recorder. The injection is placed where the maximal EMG recording can be found within the muscle. This technique ensures that the injection is at the point of the muscle that is contributing the most to the muscle activity. With routine injections and practice many centers have obtained satisfactory results without EMG guidance. [28]

Few side effects, both serious and more benign have been reported with BoNT-A administration. As injections are local, intramuscular systemic complications are rare. Injection for cervical dystonia might cause dysphagia and increased risk of aspiration pneumonias and injections for strbiamus might lead to ptosis and diplopia.[4] Other adverse events include cough, fever, upper respiratory infection, flu-like malaise, headache, and very commonly, injection site reactions (erythema, swelling) and bruising. Hypersensitivity reactions such as edema and dyspnea have been also noted. One case of anaphylaxis has been reported. Similarly spontaneous death after Botox injection has been reported but no clear causal relation proven. A meta-analysis of controlled trials for BoNT efficacy in a variety of conditions concluded that focal weakness localized to the area of injection were the only consistent events which were not reflected in controls. [26] Generally, these events were mild to moderate in severity, temporary, and related to the medication's mechanism of action.

BoNT in Neurological problems

Athough botulinum toxin is one of the most deadly neurotoxins known, the therapeutic administration of BoNT-A is quite safe. Botulinum neurotoxins act through a multistep process which involves binding to nerve terminals followed by internalization and inhibition of release of calcium-dependent neurotransmitters.

A local injection of botulinum toxin is a well-accepted treatment for focal dystonias, hemifacial spasms and strabismus. Its use by skilled neurologists has been reported to be safe and effective for the treatment of certain movement disorders[15], including blepharospasm, hemifacial spasm, oromandibular dystonia, cervical dystonia[12], focal limb dystonias[22], laryngeal dystonia, tics, and essential tremor.[19] Because of its action at the neuromuscular junction leading to reversible alteration in muscle tone and selective functional denervation of muscles, BoNT is used extensively in disorders of muscle overactivity, such as facial movement disorders, limb and

neck dystonias, and spasticity. Botulinum neurotoxins are also effective at inhibiting acetylcholine release at sites other than neuromuscular junction, leading to effective treatments for hypersecretory syndromes, especially hypersalivation and hyperhidrosis. Apart from these, recently, painful syndromes such as chronic migraine headache, low back pain, trigeminal neuralgia and some chronic conditions that respond only partially to medical treatment are also being treated with success by BoNT-A injections. It seems to be a promising alternative to some surgical interventions like sphincterotomy in patients with chronic anal fissures and detrusor overactivity. The list of possible new indications is rapidly expanding. BoNT-A for perioperative pain, treatment for amputation stump-related and phantom-limb pain, plantar fasciitis, carpal tunnel related-pain, and even refractory restless-legs syndrome are being reported.

Effective management of blepharospasm with BoNT-A was established largely via small, uncontrolled, open-label trials[33] before United States FDA approval. Review of pooled case-controlled data of over 2500 patients demonstrated a 90% efficacy rate of BoNT-A injections in blepharospasm .[20] A meta-analysis involving BoNT-A revealed only one single well-designed, prospective, blinded, placebo-controlled trial of 11 patients, in addition to many larger open-label trials, and concluded that the medication is safe in HFS and supported the conclusions of other uncontrolled studies that efficacy ranges from 76%–100%.[6,39] Peak effect was reported at 2 weeks and effect duration was nearly 3 months.[39]

Many clinical trials of BoNT-A have focused largely on occupational dystonias, especially writer's cramp[18]. Most studies were open-label, case-controlled, or reports of clinical experience with a number of patients. In one double-blinded, placebo-controlled trial, 12/20 patients with writer`s cramp sufferers experienced improved pen control after BoNT-A injections, but only 4/20 noted improved writing ability.[38] A prospective study of 47 patients assessed after BoNT-A injection concluded that patients with forearm pronation and flexion dystonias had the most improvement of their writer`s cramp symptoms.[8] Clinical experience suggests that most patients (75%–80%) have onset of benefit one week following BoNT-A injection with peak at two weeks, and effect lasting for around 3 months.[7] Leg and foot dystonias are far less common and less well-studied. Case series of primary foot dystonia patients showed improvement to repeated BoNT-A injections in 6/8.

Central nervous system disorders with upper motor neuron dysfunction often produce spasticity and hypertonia of the limb. [21] The muscles most prominently affected are those innervated by the pyramidal tracts. In the upper extremities, the shoulder adductors, elbow flexors, wrist pronators, finger and thumb flexors are most involved .In the lower extremities, hip adductors, knee extensors, and ankle plantar flexors and inverters may have increased spastic tone.[29] The most common causes of such spasticity in adults are trauma, stroke, and multiple sclerosis, while in children, cerebral palsy (CP) is the primary cause. Similar to dystonias, oral medications may have some benefit on such spasticity, but produce sedation or other cognitive side effects. [9]

In this regard, BoNT-A has been studied widely as a spasticity treatment in adults. Most studies have assessed pre- and post-treatment muscle tone via Ashworth scores. Many were performed in conjunction with electrical stimulation, and physical or occupational therapies. Brashear et al and Simpson have reported Upper limb tone improvement in blinded, placebo-controlled studies with 200–300U BoNT-A.[3,37] Similarly Lower extremity tone improved in spastic patients after BoNT-A injection, especially hip adductors and calf spasticity.[17,23] Various studies and experiences show that motor function may be improved in a select subgroup of patients who retain selective motor control and some degree of dexterity in important distal muscles, require injection of relatively few target muscles, and especially if combined with other interventions such as extensive physical therapy post injection.[35] For better results, consideration must be made of the total number of muscles to be injected and the maximum recommended dose per injection session.

In 2002, Micheli et al reported the successful treatment of a patient with hemifacial spasm associated with TN with onabotulinumtoxin A, which opened up new possibilities for its use. [24] After that, several other open-label trials have examined the preventive effects of BTX-A on TN with good results. [24, 27, 1, 30] It has been reported that direct infusion of botulinum toxin-A *in vivo* has shown to inhibit enzymes responsible for hippocampal cell death following induced seizures in rats. This shows that in addition to its role at the neuromuscular junction and peripheral nerve, BoNT-A may be a neuroprotective agent for the central nervous system also.[15,28] With all the current interest, speculation and ongoing researches in botulinum neurotoxins, we can expect emergence of exciting newer therapeutic applications to come to light in the days to come.

Thus, BoNT is a useful symptomatic treatment for many neurological disorders, and is emerging as one of the leading modes of treatments in the new subspecialty in neurology called "Interventional neurology."[14] A precise knowledge and understanding of the functional anatomy of the muscles is absolutely necessary to correctly use botulinum toxins in clinical practice. Adverse effects of

BoNT are usually mild and transient. The most common complication is excessive or unwanted weakness but this resolves as the action of the toxin is lost.

In our experience, we have used botulinum toxin-A injections successfully in variety of neurological problems like poststroke spasticity, blepharospasm, hemifacial spasm, cervical dystonias, chronic migraine, trigeminal neuralgia, writer's cramp with very good results. Use of BoNT-A needs to be encouraged in our country to provide relief to the patients suffering from many of the chronic disabling neurological problems.

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