New and emerging indications of botulinum toxin therapy

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ABSTRACT  
Botulinum neurotoxin (BoNT) is composed of the heavy chain with the receptor-binding site and the translocation domain and the light chain with endopeptidase activity that cleaves the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex, an essential molecule for membrane fusion. Its extraordinarily high toxicity depends on the affinity of the receptor-binding site to the receptor located inside the synaptosome. The membrane fusion mechanism is important not only in neurotransmitter release at the nerve terminals but also in the expression of pain receptors on the cell surface. Based on these mechanisms, BoNT is increasingly used for varieties of conditions including cosmetic uses, muscle hyperactivity, hyperhydrosis, pain, overactive bladder and epilepsy. It will become a major arm of neuromodulating treatments for neurological diseases. A part of this toxin, such as the heavy chain, may become a novel drug-delivery system for neurodegenerative diseases.

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1. Advances in botulinum toxin research

Botulinum neurotoxins (BoNTs) are produced by anaerobic bacteria of the Clostridium group and are the most potent toxins known to date [1]. There are seven serotypes of BoNTs, indicated by letters from A to G. Each toxin is composed of a heavy (H, 100 kDa) and a light chain (L, 50 kDa) linked by a disulphide bond and non-covalent interactions. The carboxy terminus of the heavy chain (HC) binds with extraordinary specificity to nerve terminals. Following receptor-mediated endocytosis and acidification of the endosome, the amino-terminal portion of the heavy chain (HN) translocates the L chain across the vesicular membrane into the cytosol. The L chain acts as a Zn$^{2+}$-dependent endopeptidase to cleave essential protein components of the neurotransmitter release machinery, the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) proteins. This disrupts Ca$^{2+}$-triggered fusion of synaptic vesicles (SVs) with the plasma membrane [2].

The receptors of BoNTs have been clarified recently: serotype B BoNT binds to synaptotagmin II$^4$ and serotype A to SV2 [4], both of which are located on the inner surface of the synaptosome. BoNT also recognises the ganglioside moiety (trisialoganglioside, GT1b) on the surface of the cell membrane, which determines the target selectivity [3]. These findings explain the activity-dependent action of the toxin: BoNTs affect the synapses most active in releasing the neurotransmitters because they can access the synapses or neuromuscular junctions with the receptors inside the vesicle. It has been known that the action of BoNTs is optimised when the muscles are activated immediately following the injection [5]. This action is in contrast with the neurolytic therapies, such as phenol injections, which affect all the nerve endings irrespective of the activities, resulting in unwanted weakness of the injected muscles. By contrast, BoNTs abolish only twitching muscles in case of hemifacial spasms. This is relevant with other involuntary movements or spasticity, where active engagement in the affected movement or posture is encouraged after injections, to attain the maximum benefit of BoNTs.

The potency of the toxin is mostly due to its very high affinity to the receptors. The receptor-binding capability of the heavy chain is now being explored for development of the drug-delivery system to neurons after replacing the L chain with other moieties [6]. Such an attempt may be fruitful for the development of drugs for amyotrophic lateral sclerosis, if the L chain is substituted by neurotrophic factors.

Types A, B and F toxins have been used for clinical settings in the past [7]. Currently, types A and B are marketed. Among type A toxins, four subtypes (A1–A4) exist, and all the marketed toxins are from subtype A1. Recently, type A2 toxin has been used in animals [8] and showed greater potency in producing weakness and less spreading into uninjected muscles than conventional A1 toxin. It was also shown that type A toxins affects central synapses, and subtype A2 has less central actions than A1 because of the less retrograde transport of the toxin to the spinal cord [9]. These findings may lead to a BoNT preparation used for larger muscles, such as those in the lower extremities in patients with spasticity.
2. Clinical indications

Indications of BoNTs have been constantly expanded in the past decade. 
BoNTs’ most popular use is for cosmetic purposes. It is widely accepted that wrinkles on the face go away almost indefinitely after the injection, but the exact mechanism is still elusive.

2.1. Muscle hyperactivity

By far the most important use in neurological diseases is for muscle hyperactivity, including dystonia and spasticity. Focal dystonias, such as blepharospasm and cervical dystonia, are the best indications among dystonias. Task-specific dystonias including writer’s or musician’s cramp are less optimal [10] because of the unwanted weakness for the tasks. Larger doses are required for treating truncal or lower-extremity dystonias, and new preparations, such as the A2 subtype, might be relevant. Generalised or segmental dystonias are treated more efficaciously by surgical manoeuvres, such as deep-brain stimulation of bilateral GPI.

Hemifacial spasms are also good indication of BoNTs, and decompression surgeries are becoming obsolete as the first-line treatment. The dose required is usually less than that in blepharospasm, and the injection interval is longer.

Spasmodic dysphonia, a dystonia involving vocal-cord muscles, is also a superb indication of BoNT. A special injection technique for treating truncal or lower-extremity dystonias, and new preparations, such as the A2 subtype, might be relevant. Generalised or segmental dystonias are treated more efficaciously by surgical manoeuvres, such as deep-brain stimulation of bilateral GPI.

Spasticity is probably one of the most prevalent and important health problems in developed nations. Up to 65% of the patients who survived stroke suffer from it. Cost of care for those patients far exceeds 2,000,000,000,000 yen or 20 billion US dollars per year in Japan. Until 2004, a few randomised controlled trials have reported some promising results in support of reduced muscle tone following BoNT injections [11]. Further research incorporating larger sample sizes, rigorous methodology, measurement of upper-limb function and functional outcomes was essential. Since then, there have been several large-scale clinical trials for upper-limb spasticity showing functional improvements [12]. A recent study in the post-stroke lower-limb spasticity also reported markedly significant improvements in the modified Ashworth scale [13]. Functional improvements were only attained by repeated injections. By now, uses in spasticity in upper and lower-limbs have been approved in UK, France, Germany and Japan, and use for upper-limb was approved by the Food and Drug Administration (FDA) in USA.

Interestingly, patients with upper-limb spasticity often improve their motor disturbance after BoNT injection and rehabilitation almost permanently, without the need for further injections. This is unlike those with hand dystonia, who need repeated injections to maintain the benefit. It is argued that BoNT may enhance synaptic reorganisation directly by its central action or indirectly through alteration of muscle afferents [14]. Another possibility is that release of the affected hand into active movements may reverse abnormal interhemispheric inhibition from the unaffected cortex to the affected.

Because the sudomotor sympathetic fibres are also cholinergic, BoNTs have been used for controlling hyperhidrosis, which can occur either after skin incisions or without any known causes.

2.2. Pain

A breakthrough in the clinical application of BoNT is its use for controlling pain and migraine. BoNT was shown to decrease the expression of pain-sensitive vanilloid receptors (e.g., transient receptor potential cation channel subfamily V member 1, TRPV1), which are up-regulated in sensitised sensory neurons [15]. This is because those receptors are expressed to the cell membrane through the fusion mechanism mediated by the SNARE complex, the substrate of BoNTs.

It was accidentally found that BoNT injection into corrugator muscle for removing skin furrows brought about a decrease in the number of migraine attacks. Since then, a number of clinical trials with a small number of cases and modest doses have resulted in equivocal results for migraine. Recently, clinical trials with larger number of cases and doses of BoNT have successfully reduced the number of attacks [16–18], followed by its approval in UK and USA.

Intractable pain or complex regional pain syndrome is another important indication recently added. Patients with these conditions present with oedematous, painful and immobile limb with skin areas with allodynia, or abnormally induced pain after light touch. Repeated injections into these areas subcutaneously result in gradual improvement of allodynia and pain, followed by decreased oedema and increased mobility. It was also found that post-stroke pain including thalamic pain also responds to subcutaneous BoNT injections made into areas with allodynia [19].

2.3. Overactive bladder (OAB)

Urinary problems are very common in the elderly. Many people are affected by urinary urgency, which can be highly bothersome. Urgency is the cornerstone symptom of overactive bladder (OAB), commonly occurring in conjunction with urinary frequency and nocturia. Once other medical causes of similar symptoms have been excluded, first-line OAB management comprises fluid-intake advice and bladder training, supplemented by antimuscarinic drugs, if necessary. BoNTs are currently explored as an alternative therapy [20,21]. The injection into the inner surface of the bladder was shown to down-regulate the expression of TRPV1 and muscarinic AcH receptors, which trigger destruors. Despite the technical difficulties, this technique will be widely used for these patients in the near future.

2.4. Epilepsy

Experimental pieces of evidence suggest that BoNT suppresses glutamate release in the central nervous system (CNS). Because of its activity-dependent action, BoNT may be used for managing intractable epilepsies [22,23]. Abnormal excitation at the epileptic foci is associated with large glutamate-induced excitatory postsynaptic potentials (EPSPs) that drive cortical neurons for lateral spread. BoNT would selectively suppress these active neurons, leaving the rest of the neurons unaffected. It would therefore be expected that BoNT suppresses neurons at the foci, while the rest of the neurons function normally. This method may become a substitute for surgical resections of the affected brain tissue. The largest problem would be the drug-delivery, and stereotactic device and cerebrospinal fluid (CSF) injections are now being contemplated.

In conclusion, BoNT is increasingly used for varieties of conditions including cosmetic uses, muscle hyperactivity, hyperhidrosis, pain, OAB and epilepsy. It will become a major arm of neuromodulating treatment for neurological diseases.

References


