

Therapeutic Uses of Botulinum Toxin

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Abstract

The most poisonous substance known to man, botulinum toxin has successfully established itself as a therapeutic agent over the years. Initially used to treat strabismus, botulinum toxin is now an accepted treatment in a wide spectrum of disorders and has over a 100 potential medical applications. The somewhat loosely-applied term 'wonder drug' could not be better employed to describe the remedial potential of this agent. With time, and through further studies, it is likely that the number of conditions treated with botulinum toxin will keep expanding. This review will focus on the mechanisms of action of botulinum toxin and the evidence behind its use in a variety of conditions.

Keywords: Botox; Botulinum Toxin; Therapeutic Uses of Botox

Introduction

Famous nineteenth century physiologist Claude Bernard, in his publication entitled *La Science Expérimentale*, described the use of poisons as 'a means for the destruction of life or as agents for the treatment of the sick' [1]. Indeed, over the years, various naturally-occurring toxins from plants, animals and micro-organisms have emerged as therapeutic agents. Tubocurarine, derived from the South American plant *Chondrodendron tomentosum* [2] was first used as an arrow poison [3], and is now used adjunctively in anaesthesia [4]. Captopril was developed from snake venom [3] while digoxin, a plant toxin, has been used for the management of heart failure for several years [5]. Newer medications such as eptifibatid and tirofiban, both used as anti-platelets, also originate from snake venom [3].

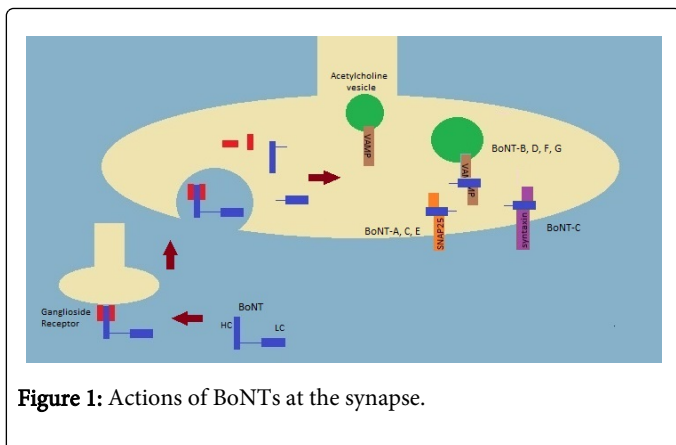
Perhaps the most resounding success comes from the use of botulinum neurotoxin (BoNT) in a range of disorders. Its transition from food poison to medical remedy is quite remarkable. Food-borne botulism accounted for many deaths across Europe in the 18th century, where it was termed 'sausage poisoning' [6]. In fact, the word *botulus* is Latin for sausage. German medical officer J. Kerner was the first to provide accurate descriptions of food-borne botulism but also to recognise its potential therapeutic uses [7]. The pathogen was identified in 1897 [8] and, not long after, a second BoNT serotype was discovered. By 1936 botulinum toxin type E had been discovered [7]. BoNT was initially experimented in animals in 1973. First used in humans for the treatment of strabismus in the late 1970s, BoNT eventually gained approval for this indication from the Food and Drug Administration (FDA) [9] and has since been endorsed for the treatment of several other conditions. This article reviews the evidence behind the common non-cosmetic applications of BoNT in various disorders, including its off-labelled uses.

Mechanisms of action

BoNTs are produced by the bacillus *Clostridium botulinum* under anaerobic conditions [10]. There are seven known serotypes classified

A to G, based on their immunological properties [11]. Once synthesised, the inert single chain polypeptide is cleaved to form toxins that consist of a heavy chain (HC) and a light chain (LC), the former being responsible for uptake in the cytosol [12]. Whether ingested or injected into muscles, BoNTs are transported to neuromuscular junctions [13]. BoNTs are internalised by binding to different gangliosides, namely synaptic vesicle-2, synaptotagmin I or synaptotagmin II [14-17]. Botulinum neurotoxins (BoNTs) then cleave soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor (SNARE) complex in motor neurons. SNARE molecules are the major components of the mechanism that mediate the fusion of synaptic vesicles with the presynaptic plasma membrane, resulting in the release of neurotransmitter [18]. The LC of BoNT-A, and E specifically cleaves synaptosome-associated protein of 25 kDa (SNAP25), preventing neurotransmitter release, while BoNT serotypes B, D, F, and G target synaptobrevin, a vesicle-associated membrane protein (VAMP) [19,20]. BoNT-C cleaves both SNAP25 and another plasmamembrane-anchored SNARE called syntaxin [19,20]. These steps are shown in detail in Figure 1. The SNARE complex is essential for acetylcholine release at the presynaptic nerve endings [21]. This inhibition results in flaccid paralysis. Recovery occurs as a result of sprouting of nerve terminals, thus re-establishing synaptic contacts [22]. This takes around 3 months, which is usually the duration after which return of clinical function is seen after botulinum toxin has been injected in a muscle.

The toxin also inhibits release of acetylcholine in all parasympathetic and cholinergic postganglionic sympathetic neurons, sparking interest in its use in overactive smooth muscles and glands [23]. Although it is clear that part of the analgesic properties of BoNTs are due to its ability to block acetylcholine release, other proposed mechanisms of pain relief include direct effects on nociceptors, influence on sensitizing mediators, alteration of afferents derived from muscle spindles, physiological changes in reflex and synergistic movements, direct and secondary autonomic effects, and neuroplastic changes in the processing of afferent somatosensory activity at multiple levels of the neuroaxis [24]. BoNTs are effective in pain syndromes due to increased muscle tone, but there is evidence that this can be achieved without a change in muscle tone [25].



Synaptic vesicles are filled with neurotransmitter, in this case acetylcholine, and stored in the cytoplasm. The heavy chain (HC) portion of different botulinum neurotoxins (BoNTs) binds to different ganglioside receptors resulting in the uptake of the whole molecule into the cytoplasm. The disulfide bond between the light and heavy chains is then cleaved. The light chain (LC) of the seven types of BoNT then binds and cleaves different proteins of the SNARE complex, namely VAMP, SNAP25 and syntaxin, to prevent release of acetylcholine at the presynaptic nerve ending.

Neurological Disorders

Cervical dystonia

Cervical dystonia, the commonest form of focal dystonia, is characterised by involuntary contractions of cervical muscles, resulting in abnormal head postures and movements, and is often associated with pain [26]. The benefits of botulinum toxin A in the treatment of cervical dystonia was first demonstrated in 1986 [27]. Its use for this condition is supported by several studies, yet only a few are class I studies [28-30]. Truong et al. conducted a randomised double-blind placebo-controlled trial involving 80 patients assigned to either botulinum toxin A or placebo injections [28]. A positive response was seen in 38% of those in the treatment arm compared to 16% in the placebo group. The FDA approved the use of botulinum toxin A for cervical dystonia in 2000 and it is the first-line treatment for this condition. However, despite the use of botulinum toxin in cervical dystonia for over 20 years, there are still unanswered questions surrounding optimal dosing and dosing intervals [31]. Treatment failure is reported in 20% of patients [32]. Adverse effects in the form of dysphagia, neck weakness, dry mouth, dysphonia and injection site pain are usually mild and transient [31].

Blepharospasm

Blepharospasm, characterised by excessive involuntary contractions of the muscles surrounding the eyes, has been treated with botulinum toxin for years. Injections are applied to the overactive orbicularis oculi muscles. It was approved for this indication in 1989 by the FDA, and this was largely based on open-label studies but given that the improvement was so striking, randomised controlled trials were deemed unnecessary [33]. Class I studies were nevertheless carried out and confirmed its efficacy [34-36]. Jankovic et al. randomised 109 patients to either incobotulinumtoxinA or placebo in a 2:1 ratio [34]. Patients in the treatment arm experienced a significant improvement

based on both objective and subjective measurements [34]. Side effects including ptosis, blurred vision and incomplete closure of the eyelid are usually well-tolerated and been found to occur with higher frequency with the use of higher doses of Dysport (120 U/eye group) than with lower doses (80 U/eye group), the latter providing the best balance of safety and efficacy [37].

Oromandibular dystonia

Oromandibular dystonia (OMD) refers to contractions of the masticatory, facial, and lingual muscles, causing repetitive and sometimes sustained jaw opening, closure or deviation in isolation or in any combination of these [38]. Evidence for the use of botulinum toxin in this setting initially came from a small randomised controlled trial showing an improvement in 37.5% of patients [39]. Further open-label studies confirmed this benefit [40,41]. In a 10 year follow-up of 162 patients with OMD treated with botulinum toxin A, it was found that jaw closing dystonia responds better and treatment was safe and effective [38].

In a longitudinal follow-up of 89 patients treated with botulinum toxin for dystonia (cervical dystonia, blepharospasm and oromandibular dystonia), prolonged and sustained therapeutic benefits with repeat injections were seen over time [42]. The mean duration of follow-up was 18.5 years and a total of 4133 visits were recorded. Approximately 10% of the visits noted side effects for cervical dystonia, 9.5% for blepharospasm and 7% with oromandibular dystonia. Tolerable adverse effects were reported in 19% of patients. These data, which arise from the longest follow-up and largest series of dystonia treated with botulinum toxin, confirm the long-term efficacy and safety of botulinum toxin.

Other forms of dystonia

Botulinum toxin is also an effective treatment for spasmodic dysphonia and limb dystonia. A retrospective analysis over 12 years involving 900 patients treated with botulinum toxin for adductor spasmodic dysphonia (ADSD), abductor spasmodic dysphonia and adductor breathing dysphonia showed an average benefit of 90% of normal, lasting an average of 15.1 weeks in the ADSD patients, and an average of 66.7% of normal function lasting an average of 10.5 weeks in the abductor patients [43]. Early evidence of the benefits of botulinum toxin for writer's cramp appeared after 20 patients were treated in a double-blind placebo-controlled trial [44]. In a randomised placebo-controlled trial involving 39 patients who were followed for 1 year, 70% of those receiving botulinum toxin A reported an improvement and therefore continued treatment compared to 31.6% in the placebo group [45]. Hand weakness was common, but transient, and reported in 18 of the 20 patients receiving botulinum toxin.

Hemifacial spasm

Hemifacial spasm is usually caused by an aberrant artery abutting the facial nerve. Microvascular surgery, which can result in complete resolution of symptoms, is restricted by potential complications associated with surgery. Symptomatic treatment with botulinum toxin is therefore first-line for this condition. Evidence for its efficacy arises mainly from open-label studies and small placebo-controlled trials. Yoshimura et al. investigated the effectiveness of botulinum toxin in 11 patients and 79% reported a subjective improvement [46]. A Cochrane review concluded that, despite a lack of good quality

controlled data, the evidence from the available studies is sufficient to suggest that it is effective and safe [47]. It gained FDA approval in 1989. Transient facial weakness is a very common and tolerable side effect.

Spasticity

Spasticity can result from various aetiologies including spinal cord injury, stroke, multiple sclerosis (MS) and cerebral palsy. There are ample class I studies to support the use of botulinum toxin for the treatment of spasticity, and also for the use of different forms of botulinum toxin [48-52]. A randomised double blind, placebo-controlled trial, including 58 patients with upper limb spasticity due to stroke, assessed the effects of botulinum toxin A in a total dose of 1000 units [48]. An improvement was shown in 92.3% of patients in the treatment arm compared to 50% in the placebo group. The effect was sustained for at least 16 weeks. There is also evidence that the benefits are dose-dependent [50]. However, most of the studies involve patients with post-stroke spasticity and cerebral palsy [53]. Few randomised controlled trials have looked at the efficacy of botulinum toxin for the treatment of spasticity in MS [54]. The FDA has approved the use of botulinum toxin for increased muscle stiffness in the elbow, wrist, and finger muscles in adults with upper limb spasticity. In the UK, Botox, Xeomin and Dysport all have a marketing authorisation for use in upper limb spasticity while only Botox has one for lower limb spasticity [55]. NICE is in the process of appraising the use of botulinum toxin A for treating upper and lower limb spasticity associated with stroke [55].

Chronic Migraine

Chronic migraine (CM), a highly disabling disorder, affects around 1-2% of the population [56], and is defined as a headache on ≥ 15 days per month for ≥ 3 months, of which ≥ 8 days meet the criteria for migraine with or without aura or responds to migraine-specific treatment [57]. The benefits of botulinum toxin in migraine initially surfaced when patients were treated cosmetically for wrinkles. Its efficacy in migraine prophylaxis was subsequently demonstrated in several trials [58-60]. Its role and efficacy in the treatment of chronic migraine was established by the phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trial [61]. In this randomised double-blind controlled trial, 1384 patients were assigned to either OnabotulinumtoxinA or placebo. Those in the treatment arm experienced a statistically significant reduction in the number of headache days, migraine days, headache episodes and migraine episodes. The FDA in the USA and Medicine and Healthcare Product Regulatory Agency (MHRA) in the UK endorsed the use of botulinum toxin for CM prophylaxis in 2010 and was later approved by NICE in 2012 on the National Health Service (NHS) in the UK. Follow-up data from patients who received all 5 treatment cycles in the PREEMPT program showed a cumulative benefit over time and that the treatment was safe and effective [62]. A high placebo rate has been pointed out in the PREEMPT trial, and observers have criticised the 10% additional benefit over placebo. However, new data from a prospective analysis of 254 patients in a real-life setting confirmed the reduction in headache and migraine days using the Headache Impact Test (HIT-6) [63]. Botulinum toxin for the prophylaxis of chronic migraine is well tolerated. Adverse reactions are usually transient and include ptosis, muscle weakness, neck pain and neck stiffness [64]. What remains to be answered is whether a subset of patients is more likely to respond and further studies will probably tackle this.

Disorders of Secretion

Hyperhidrosis

Primary hyperhidrosis is characterised by excessive and uncontrollable sweating, and can affect up to 3% of the population [65]. It affects predominantly the axillae, palms, soles of the feet and face causing considerable social problems. Systemic medications have limited efficacy while surgical approaches are reserved for extreme cases due to the risks of complications [66].

There are two class I studies supporting the use of botulinum toxin A in axillary hyperhidrosis [67,68] and several class II studies. A randomised double blind placebo-controlled trial, involving 136 patients with axillary hyperhidrosis who received botulinum toxin in one axilla and placebo in the other, found that 98% of the botulinum toxin-treated axillae showed a significant reduction in sweat production on gravimetric assessments [67]. At four weeks, 81.4% of patients reported excellent tolerance to the treatment [67]. The efficacy of botulinum toxin can be expected to last up to 9 months. Long term data from a prospective study which recruited 207 patients, of which 174 completed the 16-month study, show that botulinum toxin is safe and effective for this indication [69]. The most common side effects were the common cold and flu-like symptoms.

There are no class I study for the use of botulinum toxin in palmar hyperhidrosis. The evidence stems from class II studies, only two of which are small placebo-controlled trials. Lowe et al. randomised 19 patients to botulinum toxin A to one hand and placebo to the other [70]. Treatment success was reported in 100% of those who had botulinum toxin while only 12% rated placebo injection as successful [70]. These results were also supported by gravimetric measurements of sweat production. In a randomised double-blind study comparing Dysport® versus Botox® in primary palmar hyperhidrosis, 8 patients received Dysport® in one hand and Botox® in the other, using a 4:1 conversion ratio [71]. At 1 month, there was no statistical difference between the two treatments but at 3 months the benefits of Dysport® were significant compared to Botox®. However, no definitive conclusion can be drawn from this study due to the small sample size.

Excessive sweating induced by the ingestion of food or drink is termed gustatory hyperhidrosis. There is limited evidence supporting the use of botulinum toxin in this setting, arising mainly from case series.

Sialorrhoea

Sialorrhoea or drooling occurs when there is excessive saliva in the mouth. This can be seen as an isolated disorder or as part of other neurological disorders such as cerebral palsy, amyotrophic lateral sclerosis (ALS) and Parkinson's disease [72]. There are 3 randomised placebo-controlled trials assessing the effectiveness of botulinum toxin for the treatment of sialorrhoea in children with cerebral palsy, however, all of them are small [73-75]. Alrefai et al. studied the efficacy of intraparotid injection of botulinum toxin A in 24 children with drooling secondary to cerebral palsy and found a reduction in its frequency and severity using rating scales [74].

There are only a handful of randomised placebo-controlled trials to assess the efficacy of botulinum toxin in patients with drooling secondary to PD and ALS. One of these, involving 32 patients with Parkinson's disease and drooling showed that those in the treatment arm experienced a significant reduction in drooling frequency and

saliva production compared to placebo [76]. Jackson et al. in a randomised placebo-controlled trial involving 22 patients with ALS assigned to either botulinum toxin B, found a subjective improvement in 82% in the treatment arm compared to 38% in the placebo group at 2 weeks [77].

Disorders of the Pelvic Floor

Neurogenic detrusor overactivity

One of the most common applications of botulinum toxin in urological disorders is for the treatment of detrusor overactivity, which is characterised by urinary frequency and urge incontinence. Evidence from class I trials suggest that botulinum toxin A is effective for neurogenic detrusor overactivity. Schurch et al assigned 59 patients with neurogenic detrusor overactivity (53 due to spinal cord injury and 6 due to multiple sclerosis) to 2 doses of either botulinum toxin A or placebo injections to the detrusor muscle [78]. Significant decrease in incontinence episodes, together with improvements in bladder functions on urodynamic studies, was seen in the treatment arm. Two other randomised double-blind placebo-controlled trial reported a reduction in urinary incontinence and improvement in quality of life [79,80].

Idiopathic detrusor overactivity

Evidence from class I trials also exist for the use of botulinum toxin in the management of idiopathic detrusor overactivity (overactive bladder), which affects 12-17% of the population [81,82]. In a large randomised placebo-controlled trial, 557 patients with idiopathic detrusor overactivity unsatisfactorily controlled with anticholinergic medications, were assigned to onabotulinumtoxinA or placebo in a 1:1 ratio [82]. A significant decrease in incontinence episodes was seen in the treatment arm with 60.8% reporting a positive response on the treatment benefit scale (29.2% in the placebo group). Moreover, 22.9% of patients achieved continence compared to 6.5% in the placebo group [82]. When compared with anticholinergic therapy (solifenacin or trospium) in a head to head study involving 249 patients, the mean reduction in episodes of urge incontinence per day over the course of 6 months was similar in both groups, with comparable improvements in quality of life [83]. Continence was however achieved in 27% of the onabotulinumtoxinA group as opposed to 13% in the anticholinergic group ($p=0.003$).

Other off-labelled uses of botulinum toxin in lower urinary tract disorders include detrusor sphincter dyssynergia and painful bladder syndrome. However, the evidence for these indications is lacking and further trials are required.

Ophthalmological Disorders

Strabismus

A. Scott pioneered the use of botulinum toxin in humans and its first clinical application was for the corrective treatment of strabismus as an alternative to surgery, for which it gained FDA approval [84]. In a trial involving strabismic children who had originally been operated, 47 patients were randomised to either botulinum toxin injection or reoperation [85]. There was no significant difference in motor or sensory outcomes in the two groups. However, in another comparative trial of botulinum toxin injection versus surgery for the treatment of

strabismus in adults without fusion, surgery gave considerably better results [86]. A Cochrane review published in 2012 concluded that botulinum toxin is effective in reducing the angle of deviation but there is a need for good quality trials across the varying types of strabismus [87]. Nevertheless, due to the requirement of repeated injections, it is probably best reserved for cases where surgery is undesirable.

Dry eye disease

There is some evidence that botulinum toxin can be useful in dry eye disease [88-90], although paradoxically, keratitis sicca (dry eye syndrome) can result as a side-effect of botulinum toxin injections in periocular procedures [91]. Recently, in a randomised non-controlled trial involving 60 patients with dry eyes, 36 were treated with punctal plug insertion and 24 were given botulinum toxin injections [90]. All of the 24 botulinum toxin-treated patients showed an increase in lacrimation on the Schirmer's 2 score and all reported satisfaction with their treatment compared to 72.3% in the punctal plugs group [90]. However, larger controlled trials are needed before any meaningful conclusion can be drawn.

There is also some evidence that botulinum toxin is useful in dysthyroid upper eyelid retraction, entropion, corneal protection secondary to facial paralysis and the control of synkinetic eyelid movements [91].

Gastrointestinal Disorders

Achalasia

Achalasia is a disorder of motility characterised by impaired peristalsis and the failure of the lower oesophageal sphincter (LOS) to relax [92,93]. The management of achalasia rely mainly on surgical myotomy, intrasphincteric botulinum toxin injection and pneumatic balloon dilatation [94], with other pharmacological therapy being less effective [95]. Pasricha and his colleagues were the first to use botulinum toxin in this setting [93,96]. In a double-blind placebo-controlled trial involving 21 patients with achalasia, treatment with botulinum toxin was associated with a decrease in LOS pressure and widening of the opening of the LOS [93]. However, when compared to pneumatic balloon dilatation, botulinum toxin injection has been found to lead to a shorter period of remission [95,97,98]. Moreover, the need for repeated doses makes it less cost effective than pneumatic balloon dilatation [99]. It is therefore most effective in patients who have comorbidities and where the risks associated with dilatation or surgery would be considered to be high [94].

Other off-labelled uses of botulinum toxin in gastrointestinal disorders include anal fissures, gastroparesis and sphincter of Oddi dysfunction. Further trials are needed to assess its efficacy and safety in these settings.

Conclusion

Botulinum toxin, unlike several other plant and animal toxins, has not only turned from poison to therapeutic agent, but also to potential 'wonder drug'. It has already been successfully used in an ever-growing list of neurological and non-neurological disorders. Its mechanism of action in neuromuscular blockade is well understood, however, less is known of its mechanism in relieving chronic migraine. Long-term studies in some conditions have confirmed its safety and efficacy.

Further research still needs to be carried out to clarify its efficacy in other conditions. Questions surrounding condition-specific optimal dosage and frequency of injections also need to be addressed.

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