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What is This?

An evidence-based review of botulinum toxin (Botox) applications in non-cosmetic head and neck conditions

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Summary

Botulinum toxin (Botox) is an exotoxin produced from *Clostridium botulinum*. It works by blocking the release of acetylcholine from the cholinergic nerve end plates leading to inactivity of the muscles or glands innervated. Botox is best known for its beneficial role in facial aesthetics but recent literature has highlighted its usage in multiple non-cosmetic medical and surgical conditions. This article reviews the current evidence pertaining to Botox use in the head and neck. A literature review was conducted using The Cochrane Controlled Trials Register, Medline and EMBASE databases limited to English Language articles published from 1980 to 2012. The findings suggest that there is level 1 evidence supporting the efficacy of Botox in the treatment of spasmodic dysphonia, essential voice tremor, headache, cervical dystonia, masticatory myalgia, sialorrhoea, temporomandibular joint disorders, bruxism, blepharospasm, hemifacial spasm and rhinitis. For chronic neck pain there is level 1 evidence to show that Botox is ineffective. Level 2 evidence exists for vocal tics, trigeminal neuralgia, dysphagia and post-laryngectomy oesophageal speech. For stuttering, 'first bite syndrome', facial nerve paresis, Frey's syndrome, oromandibular dystonia and palatal/stapedial myoclonus the evidence is level 4. Thus, the literature highlights a therapeutic role for Botox in a wide range of non-cosmetic conditions pertaining to the head and neck (mainly level 1 evidence). With ongoing research, the spectrum of clinical applications and number of people receiving Botox will no doubt increase. Botox appears to justify its title as 'the poison that heals'.

Introduction

Botulinum toxin (Botox) is a protease exotoxin produced from *Clostridium botulinum*. It works by blocking the release of acetylcholine from cholinergic nerve endings causing inactivity of muscles or glands. Its effects are transient and may be graded by varying the dose and frequency of administration. Botox is one of the most potent naturally occurring biological poisons and in the

past has been responsible for many accidental deaths prior to its discovery in medicine. Its first medical use was to treat strabismus in 1980. Nine years later, the cosmetic effects of the toxin on wrinkles were noted, but it was only in 2002, following Food and Drug Administration approval, that Botox gained widespread popularity as an alternative to cosmetic surgery.[1]

Recently, the therapeutic uses of Botox have expanded exponentially to include a wide range of medical and surgical conditions. This has been aided by a greater understanding of its underlying physiology as well as improved efficacy and safety. This review examines the evidence on Botox usage in non-cosmetic conditions of the head and neck.

Methods

The Cochrane Controlled Trials Register, Medline and EMBASE databases were searched from 1980 to 2012. The medical subject heading search terms were 'botox' and 'larynx' or 'dysphonia' or 'dystonia' or 'tremor' or 'oral' or 'myoclonus' or 'temporomandibular' or 'sialorrhoea' or 'bruxism' or 'oesophagus' or 'dysphagia' or 'speech' or 'face' or 'autonomic nervous system' or 'sweating' or 'torticollis' or 'pain' or 'migraine' or 'headache' or 'myalgia' or 'neuralgia' or 'nose' or 'rhinitis'. A total of 997 English language abstracts were reviewed and 88 relevant articles identified. Further references were obtained through their bibliographies. Evidence levels, based on those suggested by the Oxford Centre for Evidence-Based Medicine (Table 1),[2] are shown in the text inside [ ]. The highest level of evidence pertaining to Botox treatment for each of the ENT conditions is presented in Table 2.

Results and discussion

Laryngeal conditions

Spasmodic dysphonia
Spasmodic dysphonia is due to inappropriate glottic closure or opening due to spasm of intrinsic laryngeal muscles. Symptoms include hoarseness and strangled speech breaks (adductor type) or hypophonia and breathy voice (abductor type).[3] A meta-analysis of 30 randomized controlled trials (RCTs) involving Botox therapy in adductor spasmodic dysphonia revealed an improvement to about one standard deviation across the dependent voice-related Quality of Life (QoL) variables studied [1a].[4,5] A subsequent RCT also confirmed the beneficial effects of Botox in spasmodic dysphonia with the greatest improvements present in those patients who were most profoundly impaired [1b].[6] In addition, a recent prospective study ($n = 133$) has demonstrated a mean Voice Handicap Index improvement of 9.6% following laryngeal Botox injection in patients with spasmodic dysphonia.[7]

Essential voice tremor
Essential voice tremor is characterized by rhythmic activation of mainly the intrinsic laryngeal muscles. The voice is affected by breaks in pitch, diminished fluency and arrests. It naturally accompanies the ageing process, but may also occur with spasmodic dysphonia.[8] Electromyography (EMG)-guided Botox injection into the thyroarytenoid muscles was shown to have beneficial effect in a RCT ($n = 13$) [1b],[9] in a prospective crossover study ($n = 10$) [3b][10] and a case report [4].[11]

Stuttering or stammering
This refers to a disorder of speech-motor control in which the flow of speech is disrupted by involuntary repetitions and prolongations of sounds, syllables, words or phrases, with occasional involuntary silent pauses, collectively caused by poor coordination between lingual, labial, laryngeal and respiratory muscles. There is only one case series that has shown that intralaryngeal Botox injection improves fluency in speech therapy failures so its value in treating this disorder is questionable and requires further research [4].[12]

Vocal tics (Gille de la Tourette syndrome)
Repetitive dyskinetic movements of the laryngeal musculature lead to the production of embarrassing speech known as vocal tics. This is commonly seen in Gille de la Tourette syndrome. There is one RCT showing that Botox injections into the thyroarytenoid muscles is efficacious in reducing the frequency and urge of vocal and motor tics ($n = 18$) [2b], but the patients did not report an overall benefit from the treatment.[13–15] Again, further research is mandated to assess the efficacy of Botox for vocal tics.

Table 1

Levels of evidence based on those suggested by the Oxford Centre for Evidence-Based Medicine

Level of evidence	Type of study
1a	Systematic review (SR) (with homogeneity*) of randomized control trials (RCTs)
1b	Individual RCT (with narrow confidence interval)
1c	All or none†
2a	SR (with homogeneity*) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g. <80% follow-up)
2c	'Outcomes' Research; ecological studies
3a	SR (with homogeneity*) of case-control studies
3b	Individual case-control study
4	Case-series, case reports and poor quality cohort or poor quality case-control studies‡
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

*This refers to a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need to be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a '-' at the end of their designated level
†Met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it
‡This refers to a cohort study that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. Poor quality case-control study refers to one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders

Pain

Headache

Numerous multicentre double-blind placebo-controlled trials support the use of Botox as a prophylactic therapy for migraine [1a].[16-18] The technique involves injections into muscles innervated by the facial or trigeminal nerves (e.g. procerus, corrugator, frontalis, temporalis and suboccipital), specific sites of pain distribution or a combination of both.[19] Significant reductions from baseline were observed in patients in the Botox trial arm with regard to headache and migraine days, cumulative hours of headache and frequency of moderate/severe headache days. A recent meta-analysis confirmed these beneficial effects of Botox but only in the treatment of chronic daily headaches and chronic migraines (>15 episodes per month) [1a]. Adverse effects including blepharoptosis, skin tightness, paraesthesias, neck stiffness, muscle weakness and neck pain can occur at injection sites but these were minimal and transient.[20]

Cervical dystonia or spasmodic torticollis

This refers to sustained neck muscle contraction resulting in involuntary movements of the head and neck associated with significant cervical pain and abnormal cervical postures. It can be primary or secondary to other neurological disorders.[21] The evidence supporting the use of Botox in the treatment of cervical dystonia consists of two Cochrane systematic reviews of 13 (677 participants for Botox A) and three (308 participants for Botox B) high-quality RCTs, respectively [1a].[22,23] These meta-analyses showed that single injection of Botox is effective (as evident from both objective and subjective rating scales) and can be safely repeated if necessary. Since then, there have been further RCTs confirming the efficacy and safety of Botox in the treatment of cervical dystonia in both previously treated as well as Botox-naive patients [1b].[24] It is worth noting that Botox not only reduces abnormal movements and contractures but can also prevent secondary degenerative changes of the cervical spine and associated radiculopathy.[25,26]

Masticatory myalgia

Masticatory pain can be explained by chronic nociceptive irritation of the tendons and fascias of the masseter, temporalis and medial pterygoid muscles.[27,28] There are three RCTs showing Botox to be more effective than placebo (saline) in reducing masticatory myalgia [1b].[29-31] The most recent of these three RCTs also evaluated with EMG the action potentials of the masseter and temporalis muscles and showed that these decreased by nearly 80% on day 14, and by 25% on day 28 following Botox injection.[30] Botox causes a disuse atrophy of the affected muscle which relieves tension, improves aerobic metabolism

Table 2

Levels of evidence for the role of Botox in various head and neck conditions

Condition	Highest level of evidence
Laryngeal	
Spasmodic dysphonia[4,5]	1a
Essential voice tremor[9]	1c
Stuttering[12]	4
Vocal tics[13-15]	2b
Pain	
Headache[16-18,20]	1a
Cervical dystonia/spasmodic torticollis[22,23]	1a
Masticatory myalgia[29-31]	1b
Chronic neck pain[33] (non-beneficial)	1a
Trigeminal neuralgia[34-36]	2b
First bite syndrome[40,41]	4
Oesophageal	
Oesophageal speech postlaryngectomy[44-47]	2c
Dysphagia[51-53]	2c
Oral	
Sialorrhoea[55-57]	1b
Temporomandibular joint disorders[29,31,59]	1b
Bruxism[29]	1b
Oromandibular dystonia[63,64]	4
Palatal/stapedial myoclonus[65,66]	4
Facial	
Blepharospasm[69-71]	1b
Hemifacial spasm[75]	1b
Facial nerve paresis[76-78]	4
Nasal	
Rhinitis[79-82]	1b
Autonomic	
Frey's syndrome[85-90]	4

and enables decompression of afferent nociceptive neurons through reduction of substance P-mediated neurogenic inflammation.[31,32]

Chronic neck pain (no benefit with Botox)

Several studies have assessed the role of intramuscular Botox injections in chronic neck pain; however, no significant beneficial effect has been demonstrated. A recent Cochrane systematic review of nine trials (503 participants) showed that Botox alone was no better than the placebo (saline) for patients with subacute or chronic neck pain

and concluded that the available evidence does not support the use of Botox either as a monotherapy or in combination with any other treatment in patients with subacute or chronic neck pain [1a].[33]

Trigeminal neuralgia

The role of Botox in the treatment of drug-refractory trigeminal neuralgia has been evaluated in three studies ($n = 15$, $n = 12$, $n = 8$, respectively).[34-36] All three studies (including a low-quality RCT) found Botox to be an effective treatment with the majority of the patients reporting a reduction or even disappearance of the pain [2b].[34-36] Botox was found to be effective in combination with pharmacotherapy, prior to considering more invasive therapies such as surgery or gamma knife radiosurgery.[34] As such, Botox is a particularly valuable treatment for elderly patients and those with adverse anaesthetic comorbidities.[37,38]

First bite syndrome

This is the development of facial pain after the first bite of each meal and is seen after surgery in the parapharyngeal space, especially deep lobe parotidectomy.[39] It is probably due to autonomic dysfunction of salivary myoepithelial cells. Intraparotid Botox injection was found to significantly decrease symptom severity and improve the patients' QoL in a case series of five patients and a case report [4].[40,41]

Oesophageal conditions

Oesophageal speech post-laryngectomy

Tracheoesophageal puncture in laryngectomy patients allows excellent quality speech development in most cases. The procedure involves cricopharyngeal myotomy and valve placement. However, postoperative pharyngo-oesophageal spasm can cause failure of tracheoesophageal speech and dysphagia.[42] Traditionally, this was treated with dilation of the pharyngo-oesophageal segment (POS), pharyngeal myotomy and/or pharyngeal neurectomy.[43] More recently, EMG-guided Botox administration that chemically denervates the cricopharyngeus muscle facilitating tracheoesophageal speech and relieving dysphagia has been reported. There are several

prospective[44–47] and retrospective outcomes research studies[48] assessing the efficacy of Botox using both subjective (videotaped recordings) and objective (videostroboscopy) outcome measures [2c]. In corroboration, the largest and most recent prospective study consisting of 34 laryngectomized patients showed Botox therapy to be effective in POS voice restoration, especially when combined with speech therapy [2c].[44] The effects of Botox were shown to be long-lasting with only one patient needing to be re-injected every three months.[44] These results are promising but further, higher quality studies are needed to establish the true value of Botox in oesophageal speech post-laryngectomy.

Dysphagia

Incoordination of cricopharyngeal contractions at the initiation of swallowing can result in dysphagia, especially in the elderly population. EMG-guided Botox injections either percutaneously[49] or endoscopically[50] to the cricopharyngeus muscle were found to be effective in the treatment of dysphagia in a number prospective and retrospective outcomes research studies [2c].[51–53] Effective toxin administration can predict a successful surgical outcome following cricopharyngeal myotomy.[51,54] Again, like with oesophageal speech post-laryngectomy, these results are promising but further, higher quality studies are needed before the true value of Botox in dysphagia is determined.

Oral conditions

Sialorrhoea

Sialorrhoea may occur in neurological and other akinetic disorders such as Parkinson's disease and cerebral palsy. There are several RCTs where the efficacy of Botox injections to the parotid and/or submandibular glands in such patients has been demonstrated [1b].[55–57] The effects last 3–6 months and can be repeated. Injections can also be used for sialorrhoea caused by salivary fistulas and sialadenitis.[58]

Temporomandibular joint disorders

Spasm of the lateral pterygoid muscles may cause temporomandibular joint (TMJ) disc displacement anteriorly resulting in exquisite pain and clicking.

The evidence supporting the use of Botox in the treatment of such TMJ disorders includes multiple RCTs [1b].[29,31,59] However, injection of Botox into the lateral pterygoid muscle may cause a 'fixed' smile due to diffusion into the superficial facial muscles.[60]

Bruxism

This is characterized by non-functional contact of the mandibular and maxillary teeth resulting in clenching or tooth grinding due to repetitive, unconscious contraction of the masseter and temporalis muscles.[61] There is one RCT ($n = 30$) which has shown Botox to be efficacious in reducing myofascial pain symptoms in bruxers compared with control patients receiving saline placebo injections[29] with a second one currently underway [1b].[62]

Oromandibular dystonia

This disorder is characterized by involuntary, action-induced, tonic or clonic spasms of the masticatory, lingual and pharyngeal musculature. Symptoms include dysphagia, dysarthria, bruxism and tempomandibular joint subluxation. There are case series and case reports [4] showing favourable effects of Botox injections into the lateral pterygoid, anterior belly of digastric, masseter and temporalis muscles.[63,64] Thus, further higher quality studies are needed to establish the true role of Botox in the treatment of oromandibular dystonia.

Palatal and stapedius myoclonus

Palatal myoclonus is characterized by involuntary palatal contractions, causing clicking tinnitus due to the action of soft palate muscles on the membranous Eustachian tube. Similarly, stapedius myoclonus can cause clicking tinnitus due to the contractions of the stapedius muscle. There are two case reports, one for each type of myoclonus where the use of Botox has been shown to be beneficial in relieving the patients' symptoms [4]. For palatal myoclonus, Botox was injected in the soft palate under EMG guidance,[65] while for stapedius myoclonus, Botox was placed trans-tympanically into the middle ear on a piece of gelfoam.[66] In the latter case, the beneficial effects of Botox lasted for four months.

Facial conditions

Blepharospasm

Involuntary contraction of the eyelid muscles typically occurs bilaterally and in patients over 60 years. The orbicularis oculi muscle is most commonly implicated, but upper facial muscles can also be affected. The therapeutic use of Botox in blepharospasm was first described in 1985[67] and it has since become the treatment of choice.[68] There are three RCTs demonstrating the superiority of Botox over placebo [1b].[69–71] A recent Cochrane systematic review has concluded that doing more RCTs to prove the effectiveness of Botox over the placebo (saline) would be unethical due to the high efficacy and obvious benefits of Botox in treating blepharospasm.[72]

Hemifacial spasm

This is characterized by unilateral, recurrent, involuntary movements of the muscles innervated by the facial nerve. It is usually due to compression of the facial nerve near its origin by an aberrant branch of the posterior inferior cerebellar artery.[73] The first study to assess Botox in hemifacial spasm was in 1986.[74] Since then, there have been several studies, including one RCT which showed Botox to be an effective and safe treatment.[75] This RCT involved 11 patients and clearly demonstrated the beneficial effect of the Botox over the placebo [1b].

Facial nerve paresis

Botox may be used to induce therapeutic ptosis, thereby protecting the cornea during the acute phase of facial nerve paresis. This is achieved by transcutaneous injection into Mueller's muscle and the levator palpebrae superioris. There are two case series of therapeutic chemodenervation with Botox of these muscles comprising three and 10 patients, respectively.[76,77] Both showed that Botox administration is beneficial in preventing damage as well as healing of the cornea [4]. In addition, there is one case series of 30 patients showing Botox to reduce synkinesis in aberrant facial nerve regeneration following facial nerve paresis.[78] In that study, Botox was injected to several synkinetic muscles of patients with facial nerve paresis and all 30 patients experienced improvement after treatment [4].

Nasal conditions

Rhinitis

In a RCT of 39 patients with allergic rhinitis, Botox therapy provided better symptomatic control than steroid injections into each inferior turbinate, both in terms of the duration and degree of symptoms [1b].[79] In another RCT of 20 patients with idiopathic (vasomotor) rhinitis, topical application of Botox on a sponge significantly reduced rhinorrhoea compared with placebo (saline) but nasal congestion remained unchanged.[80] Furthermore, in a study of 38 patients with idiopathic rhinitis, Botox displayed a similar degree and duration of efficacy with regard to hypersecretion symptoms to ipratropium bromide.[81] Middle and inferior turbinate injections of Botox were shown to be a highly effective, safe and simple intervention in a RCT of 30 patients with vasomotor rhinitis [1b].[82] Hence, the role of Botox seems promising in the treatment of allergic and idiopathic rhinitis though several limiting factors prevent its widespread use. These include the mode of administration which can be associated with the requirement of specialized skills and the potential for significant pain (particularly with injection to the inferior and/or middle turbinates) in addition to its high cost.[83]

Autonomic conditions

Frey's syndrome

This typically occurs after parotid surgery and is caused by aberrant regeneration of postganglionic parasympathetic fibres innervating sympathetic cholinergic sweat glands. The result is sweating, flushing and piloerection while eating (gustatory sweating).[84] Several case series have demonstrated the efficacy of Botox in Frey's syndrome [4].[85–90] The procedure involves injecting the areas of gustatory sweating identified by an iodine-starch test. Further research is needed to assess the efficacy of Botox as a treatment for Frey's syndrome.

Conclusion

The literature highlights a therapeutic role for Botox in a wide range of non-cosmetic conditions pertaining to Otorhinolaryngology and Head & Neck Surgery. With ongoing research, the spectrum of clinical applications and number of

people receiving Botox will no doubt increase. Botox appears to justify its title as 'the poison that heals'.

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