



REVIEW

The therapeutic usage of botulinum toxin (Botox) in non-cosmetic head and neck conditions – An evidence based review



Kamran Habib Awan *

Department of Oral Medicine & Diagnostic Sciences, College of Dentistry, King Saud University, Riyadh, Saudi Arabia

Received 7 November 2015; accepted 24 April 2016

Available online 30 April 2016

KEYWORDS

Botox;
Level of evidence;
Head and neck;
Review;
Toxin

Abstract Botulinum toxin (Botox) is an exotoxin produced from *Clostridium botulinum*. It blocks the release of acetylcholine from the cholinergic nerve end plates resulting in inactivity of the muscles or glands innervated. The efficacy of Botox in facial aesthetics is well established; however, recent literature has highlighted its utilization in multiple non-cosmetic medical and surgical conditions. The present article reviews the current evidence pertaining to Botox use in the non-cosmetic head and neck conditions. A literature search was conducted using MEDLINE, EMBASE, ISI Web of Science and the Cochrane databases limited to English Language articles published from January 1980 to December 2014. The findings showed that there is level 1 evidence supporting the efficacy of Botox in the treatment of laryngeal dystonia, 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 and trigeminal. For stuttering, facial nerve paresis, Frey's syndrome and oromandibular dystonia the evidence is level 4. Thus, there is compelling evidence in the published literature to demonstrate the beneficial role of Botox in a wide range of non-cosmetic conditions pertaining to the head and neck (mainly level 1 evidence). With more and more research, the range of clinical applications and number of individuals getting Botox will doubtlessly increase. Botox appears to justify its title as 'the poison that heals'.

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* Tel.: +966 (1) 467 7422; fax: +966 (1) 467 9018.

E-mail address: kamranhabibawan@gmail.com.

Peer review under responsibility of King Saud University.



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1. Introduction

Botulinum toxin (Botox) is a protease exotoxin produced by a Gram-positive, rod-shaped, anaerobic, spore-forming, motile bacterium called *Clostridium botulinum*. When released, it causes inactivity of muscles or glands by blocking the release of acetylcholine from cholinergic nerve endings. Although its effects are short-lived, varying the frequency and dosage of administration may alter them. Botox is a standout among the most powerful normally occurring organic toxins and in the past has been in charge of numerous inadvertent deaths before its disclosure in prescription. It was first used in medicine in 1980 to treat strabismus. Although in 1989, the cosmetic effects of Botox on wrinkles were noticed, it was only in 2002, that it gained global recognition as a potential cosmetic therapeutic agent after the approval from Food and Drug Administration (Lang, 2004).

As of late, the therapeutic uses of Botox have extended exponentially to incorporate an extensive variety of medical and surgical conditions. This has been helped by a more noteworthy comprehension of its hidden physiology and in addition enhanced efficacy and safety. This review evaluates the evidence on Botox use in non-cosmetic conditions of the head and neck.

2. Materials and methods

2.1. Search strategy

Detailed automated literature searches of MEDLINE, EMBASE, ISI Web of Science and the Cochrane databases limited to English Language articles published from January 1980 to December 2014 were conducted. The search strategy was based on the recommendation of Oxford Center for Evidence-Based Medicine. The following keywords and Boolean operators were used, 'botox' and 'larynx' or 'dysphonia' or 'dystonia' or 'tremor' or 'oral' or 'myoclonus' or 'temporo mandibular' 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'.

2.2. Data collection and extraction

Titles and abstract of the studies that fulfilled the criteria were initially screened. Full texts of the studies that were found relevant judged by the abstract were independently and manually assessed. Further references were obtained through their bibliographies.

Table 1 Levels of evidence based on the Oxford Centre for Evidence-Based Medicine.

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

^a Refers to a systematic review that is free of worrisome variations (heterogeneity) in the directions and degree of results between individual studies.

^b Refers to 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.

^c 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.

Table 2 Levels of evidence for the role of Botox in various non-cosmetic head and neck conditions.

Conditions	Highest level of evidence
Laryngeal condition	
Laryngeal dystonia (Boutsen et al., 2002; Brazeau, 2010)	1a
Stuttering or stammering (Brin et al., 1994)	4
Vocal tics (Kwak et al., 2000; Marras et al., 2001; Porta et al., 2004)	2b
Pain	
Headache (Aurora et al., 2010; Diener et al., 2010; Dodick et al., 2010; Jackson et al., 2012)	1a
Cervical dystonia (Costa et al., 2005a, 2005b)	1a
Masticatory myalgia (Guarda-Nardini et al., 2008; Kurtoglu et al., 2008; von Lindern et al., 2003)	1b
Chronic neck pain (Langevin et al., 2011)	1a
Trigeminal neuralgia (Bohluli et al., 2011; Turk et al., 2005; Zuniga et al., 2008)	2b
Oral conditions	
Sialorrhoea (Lagalla et al., 2006; Mancini et al., 2003; Ondo et al., 2004)	1b
Temporomandibular joint disorders (Guarda-Nardini et al., 2008; von Lindern et al., 2003; Dengehem et al., 2012)	1b
Bruxism (Guarda-Nardini et al., 2008)	1b
Oromandibular dystonia (Mendes and Upton, 2009; Moller et al., 2007)	4
Facial conditions	
Blepharospasm (Fahn et al., 1985; Frueh et al., 1988; Jankovic, 1988b)	1b
Hemifacial spasm (Yoshimura et al., 1992)	1b
Facial nerve paresis (Naik et al., 2008; Reddy and Woodward, 2010; Toffola et al., 2010)	4
Nasal condition	
Rhinitis (Yang et al., 2008; Rohrbach et al., 2009; Sapci et al., 2008; Ozcan et al., 2006)	1b
Autonomic conditions	
Frey's syndrome (Beerens and Snow, 2002; Cantarella et al., 2010; de Bree et al., 2009; Drobik and Laskawi, 1995; Pomprasit and Chintrakarn, 2007; Steffen et al., 2012)	4

3. Results

Initial search yielded a total of 997 English language studies. After review of the titles and abstracts, 88 studies were found relevant and are presented in this review. Evidence levels, based on those suggested by the Oxford Centre for Evidence-Based Medicine (Table 1) (<http://www.cebm.net/index.aspx?o=1025>), 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.

4. Discussion

4.1. Laryngeal conditions

4.1.1. Laryngeal dystonia

Laryngeal dystonia is caused by spasm of intrinsic laryngeal muscles resulting in unseemly closure or opening of glottis. Symptoms include hypophonia and breathy voice (abductor type) or hoarseness and strangled speech breaks (adductor type) (Rosenfield et al., 1990). A meta-analysis of 30

randomized controlled trials (RCTs) involving Botox therapy in adductor laryngeal dystonia demonstrated an improvement to about one standard deviation across the dependent voice-related Quality of Life (QoL) variables examined (Boutsen et al., 2002; Brazeau, 2010). A subsequent RCT likewise affirmed the beneficial effects of Botox in laryngeal dystonia and showed greatest improvement among those patients who were most significantly disabled [1b] (Cannito et al., 2004). Furthermore, a recent prospective study ($n = 133$) has shown a mean Voice Handicap Index improvement of 9.6% after laryngeal Botox administration in patients with laryngeal dystonia (Novakovic et al., 2011).

4.1.2. Stuttering or stammering

Stuttering or stammering is a disorder of selection, initiation, and execution of motor sequences necessary for fluent speech production. The disruption in the flow of speech is caused by poor coordination between lingual, labial, laryngeal and respiratory muscles resulting in involuntary repetitions and prolongation of sounds, syllables, words or phrases, with occasional involuntary silent pauses. There is only one case series that has demonstrated an improvement in speech fluency among patients who were administered with intralaryngeal Botox injections; therefore, its value in treating this disorder is flawed and necessitates further research [4] (Brin et al., 1994).

4.1.3. Vocal tics (*Gille de la Tourette syndrome*)

This refers to sudden, repetitive, nonrhythmic vocalization as a result of repetitive dyskinetic movement of the laryngeal musculature. This is commonly seen in Gille de la Tourette syndrome. It may range from simple vocal tics such as throat clearing, sniffing, or grunting to more complex ones such as echolalia (repeating words just spoken by someone else), palilalia (repeating one's own previously spoken words), lexilalia (repeating words after reading them), and coprolalia (the spontaneous utterance of socially objectionable or taboo words or phrases). Although there is one RCT that demonstrated that Botox injections into the thyroarytenoid muscles is effectual in decreasing the recurrence and inclination of vocal and motor tics ($n = 18$) [2b], the patients did not report a general advantage from the treatment (Kwak et al., 2000; Marras et al., 2001; Porta et al., 2004). Again, further research is required to assess the efficacy of Botox for vocal tics.

4.2. Pain

4.2.1. Headache

A number of multicenter double-blind placebo-controlled trials have demonstrated the efficacy of Botox as a prophylactic therapy for migraine [1a] (Aurora et al., 2010; Diener et al., 2010; Dodick et al., 2010). The procedure includes administration of Botox injections into muscles innervated by the trigeminal or facial nerves or specific pain distribution sites or a combination of both (Durham and Cady, 2011). Significant decrease from baseline was observed in patients in the Botox trial arm with regard to headache and migraine days, total hours of headache and recurrence of moderate/severe headache days. A recent meta-analysis affirmed these valuable effects of Botox, but only in the treatment of chronic daily headaches and chronic migraines (> 15 episodes per month) [1a]. The review also reported adverse effects including

blepharoptosis, skin tightness, paraesthesias, neck stiffness, muscle weakness and neck pain at the injection sites; however, these were insignificant and transient (Jackson et al., 2012).

4.2.2. Cervical dystonia or spasmodic torticollis

This refers to an chronic neurological movement disorder causing the neck to involuntarily turn to the left, right, upward, and/or downward resulting in significant cervical pain and abnormal cervical postures. It can be primary or secondary to other neurological disorders (Velickovic et al., 2001). The evidence supporting the utilization of Botox in the treatment of cervical dystonia comprises of two Cochrane systematic reviews of 13 (677 members for Botox An) and three (308 members for Botox B) high-quality RCTs, respectively [1a] (Costa et al., 2005a, 2005b). These meta-analyses demonstrated that solitary injection of Botox is effective (as apparent from both objective and subjective rating scales) and can be securely refreshed if needed. Since then, there have been further RCTs affirming the efficacy and safety of Botox in the treatment of cervical dystonia in both previously treated and Botox-naive patients [1b] (Comella et al., 2011). Studies have shown that Botox not only lessens irregular movements and contractures but also avert secondary degenerative changes of cervical spine and related radiculopathy (Jankovic et al., 2011; Ruiz et al., 2011).

4.2.3. Masticatory myalgia

Masticatory pain may be a result of chronic nociceptive irritation of the tendons and fascias of the masseter, temporalis and medial pterygoid muscles (Clark, 2008; Solberg, 1986). There are three RCTs indicating Botox to be more viable than placebo (saline) in lessening masticatory myalgia [1b] (Guarda-Nardini et al., 2008; Kurtoglu et al., 2008; von Lindern et al., 2003). The latest of these three RCTs additionally assessed the action potential of the masseter and temporalis muscles with EMG and demonstrated that these diminished by nearly 80% on day 14, and by 25% on day 28 after Botox administration (Kurtoglu et al., 2008). Botox causes a disuse atrophy of the affected muscle, which mitigates strain, enhances aerobic metabolism and enables decompression of afferent nociceptive neurons by decreasing substance P-mediated neurogenic inflammation (Bhagal et al., 2006; von Lindern et al., 2003).

4.2.4. Chronic neck pain

A number of studies have examined the role of intramuscular Botox injection in chronic neck pain; however, no critical advantageous impact has been illustrated. A recent Cochrane systematic review of nine trials (503 participants) demonstrated that Botox alone was no superior to the placebo (saline) for patients with subacute or chronic neck pain and reported that the available evidence does not support the utilization of Botox either as a monotherapy or in combination with any other treatment in patients suffering from subacute or chronic neck pain [1a] (Langevin et al., 2011).

4.2.5. Trigeminal neuralgia

The role of Botox in the treatment of drug refractory trigeminal neuralgia has been assessed in three studies ($n = 15$, $n = 12$, and $n = 8$, respectively) (Bohluli et al., 2011; Turk

et al., 2005; Zuniga et al., 2008). All three studies (including a low-quality RCT) observed Botox to be a viable treatment with most of the patients reporting a lessening or even vanishing of the pain [2b] (Bohluli et al., 2011; Turk et al., 2005; Zuniga et al., 2008). Botox was observed to be effective in combination with pharmacotherapy, prior to considering more invasive therapies such as surgery or gamma knife radiosurgery (Bohluli et al., 2011). As such, Botox is an especially effective treatment modality for elderly patients and those with adverse anesthetic comorbidities (Allam et al., 2005; Ngeow and Nair, 2010).

4.3. Oral conditions

4.3.1. Sialorrhoea

Sialorrhoea, defined as an overflow of saliva from the mouth (drooling), negatively affects both patient's quality of life and social interactions. It may occur in neurological and other akinetic disorders, for example, Parkinson's disease and cerebral paralysis. There are a few RCTs where the competence of Botox injections to the parotid and/or submandibular glands in such patients has been presented, with effects lasting 3–6 months and no major adverse effects [1b] (Lagalla et al., 2006; Mancini et al., 2003; Ondo et al., 2004). Likewise, Botox injections can be utilized in patients with sialorrhoea caused by salivary fistulas and sialadenitis (Ellies et al., 2004).

4.3.2. Temporomandibular joint disorders

Chronic recurrent temporomandibular joint (TMJ) dislocation is an uncommon condition that is agonizing and upsetting to patients and exceptionally trying for the clinicians. Sustained TMJ dislocation is not manageable by manual reduction alone when the etiology is muscular in nature. Spasm of lateral pterygoid muscles may result in anterior displacement of TMJ with excruciating pain and clicking. Several RCTs provide supporting evidence for the utilization of Botox in the management of such TMJ disorders [1b] (Guarda-Nardini et al., 2008; von Lindern et al., 2003; Dengehem et al., 2012). However, administration of Botox into the lateral pterygoid muscles may bring about a 'fixed' smile because of dissemination of the toxin into the superficial facial muscles (Chikhani and Dichamp, 2003).

4.3.3. Bruxism

Bruxism is described as 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 (Behr et al., 2012). There is one RCT ($n = 30$) which has demonstrated Botox to be adequate in lessening myofascial pain symptoms in bruxers compared to control patients who were administered saline placebo injections [1b] (Guarda-Nardini et al., 2008). More randomized controlled studies are needed to confirm that Botox is safe and reliable for routine clinical use in bruxism.

4.3.4. Oromandibular dystonia

Oromandibular dystonia is a focal dystonia characterized by involuntary, forceful contractions of the face, jaw, and/or tongue causing difficulty in opening and closing the mouth and often affecting chewing and speech. It is often associated with

dystonia of the neck muscles (cervical dystonia/spasmodic torticollis), eyelids (blepharospasm), or larynx (spasmodic dysphonia). Symptoms include dysphagia, dysarthria, bruxism and temporomandibular joint subluxation. There are case-series and case reports [4] showing encouraging results of Botox administration into the masseter, lateral pterygoid, and anterior belly of digastric and temporalis muscles (Mendes and Upton, 2009; Moller et al., 2007). Therefore, there is a need to carry out high-quality studies to ascertain the true role of Botox in the management of oromandibular dystonia.

4.4. Facial conditions

4.4.1. Blepharospasm

It is characterized by abnormal, involuntary, bilateral contraction or twitching of the eyelids muscles. Symptoms include Excessive blinking and spasming of the eyes, uncontrollable contractions or twitches of the eye muscles and surrounding facial area, dryness of the eyes and sensitivity to the sun and bright light. The use of Botox for the treatment of blepharospasm was first reported in 1985 and has since become the treatment of choice (Jankovic, 1988a, 1988b; Scott et al., 1985). There are three RCTs that have demonstrated the predominance of Botox over placebo [1b] (Fahn et al., 1985; Frueh et al., 1988; Jankovic, 1988a, 1988b). In a recent Cochrane systematic review, the authors reported that it would be unethical to carry out more RCTs to demonstrate the usefulness of Botox over the placebo (saline) because of the high efficacy and evident advantages of Botox in treating blepharospasm (Costa et al., 2005c).

4.4.2. Hemifacial spasm

This is a rare neuromuscular disease characterized by irregular, recurrent, involuntary muscle contractions on one side of the face. Although there are multiple theories to explain the facial nerve dysfunction found in hemifacial spasm, it is generally accepted that it is caused by compression of the facial nerve near its origin by an aberrant branch of the posterior inferior cerebellar artery (Illingworth et al., 1996). The first study to assess Botox in hemifacial spasm was in 1986 (Elston, 1986). Since then, there have been a few studies, including one RCT, which demonstrated Botox to be a powerful and safe treatment (Yoshimura et al., 1992). This RCT included 11 patients and distinctly exhibited the favorable impact of the Botox over the placebo [1b].

4.4.3. Facial nerve paresis

In acute phase of facial nerve paresis, Botox may be utilized to induce therapeutic ptosis to protect the cornea. Transcutaneous injections of Botox are administered into Mueller's muscle and the levator palpebrae superioris. There are only two case-series showing therapeutic chemodenervation of these muscles with Botox (Naik et al., 2008; Reddy and Woodward, 2010). Both demonstrated that Botox is not only useful in preventing damage to the cornea but also facilitates in the healing process [4]. Furthermore, there is one case-series of 30 patients demonstrating the efficacy of Botox to reduce synkinesis in aberrant facial nerve regeneration following facial nerve paresis (Toffola et al., 2010). In this case-series, Botox was injected to a number of synkinetic muscles of all 30

patients who had facial nerve paresis with all showing marked improvement [4].

4.5. Nasal conditions

4.5.1. Rhinitis

A number of RCTs have shown beneficial effects of Botox in patients with rhinitis. In a RCT of 39 patients with allergic rhinitis, Botox treatment demonstrated preferable symptomatic control over steroid injections into each inferior turbinate, both in terms of the duration and degree of symptoms [1b] (Yang et al., 2008). In another RCT of patients with idiopathic rhinitis, topical use of Botox showed considerable reduction in rhinorrhea in comparison with placebo (saline); however, no change was noted in nasal congestion (Rohrbach et al., 2009). In a study of 38 patients with idiopathic rhinitis, Botox demonstrated comparable results to ipratropium bromide in controlling hypersecretion symptoms (Sapci et al., 2008). In a RCT of 30 patients with vasomotor rhinitis, Botox injections in the middle and inferior turbinate were demonstrated to be simple, safe and highly effective [1b] (Ozcan et al., 2006). Although these studies provide encouraging results for the role of Botox in the treatment of allergic and idiopathic rhinitis, several limiting factors including high cost, specialized training, and potential pain prevent its widespread use (Nowak and Szyfter, 2011).

4.6. Autonomic conditions

4.6.1. Frey's syndrome

This is a rare neurological disorder resulting from damage to or near the parotid glands, and from damage to the auriculotemporal nerve often after surgery. There is aberrant regeneration of postganglionic parasympathetic fibers innervating sympathetic cholinergic sweat glands resulting in sweating, flushing and piloerection while eating (gustatory sweating) (Neumann et al., 2011). Several studies have shown the efficacy of Botox as a treatment modality for Frey's syndrome [4] (Beerens and Snow, 2002; Cantarella et al., 2010; de Bree et al., 2009; Drobik and Laskawi, 1995; Pomprasit and Chintrakarn, 2007; Steffen et al., 2012). Although Botox is acclaimed as the safest and most effective treatment for Frey's syndrome, higher quality studies involving a more significant number of patients are needed.

5. Conclusion

Botox has certainly been demonstrated to have significant value in the management of a wide range of non-cosmetic conditions pertaining to Otorhinolaryngology and Head & Neck Surgery. With more and more research, the range of clinical applications and number of individuals getting Botox will doubtlessly increase. Botox appears to justify its title as 'the poison that heals'.

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