Review Article

A BOTULINUM TOXIN- THE POISON THAT HEALS - A REVIEW ARTICLE

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Abstract:

Botulinum toxin (Botox) is an exotoxin produced from Clostridium botulinum. It blocks the release of acetylcholine from the cholinergic nerve end plates and leads to inactivity of the muscles or glands innervated. It 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. The application of Botox in oral and maxillofacial surgery began in 1982. It was used by Jan Carruthers for reducing muscle mass and smoothening skin. Each specialty approaches Botox with its medical indications.

This article reviews the evidence related to Botox used in the head, neck, and face region. A literature review was conducted using PubMed, Medline, Cochrane Controlled Trials Register, and EMBASE databases limited to English Language articles published from 1980 to 2020. The findings suggested that there is level 1 evidence supporting the efficacy of Botox in the treatment of headache, bruxism, masticatory myalgia, sialorrhoea, temporomandibular joint disorders, 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 facial nerve paresis, stuttering, 'first bite syndrome', Frey's syndrome, oromandibular dystonia, and palatal/stapedial myoclonus the evidence is level 4.

Keywords: BOTOX, NON-COSMETIC USES.

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INTRODUCTION

Botulinum neurotoxin is proving to be one of the most versatile therapies in all of medicine. It is a protease exotoxin produced by a Gram-positive, anaerobic, rod-shaped, spore-forming, motile bacterium called Clostridium botulinum. When released, it causes the inactivity of muscles or glands by blocking the release of acetylcholine from cholinergic nerve endings. Well known as a potent poison, and still responsible for many deaths from botulism worldwide each year, botulinum neurotoxin is very safe when used by a physician in carefully controlled circumstances. Since its introduction in plastic surgery for cosmetic use in the 1980s, it has been widely used in various fields, including dentistry, dermatology, ophthalmology, plastic surgery, and medicine. Ophthalmologist Alan B. Scott first identified the therapeutic potential of botulinum neurotoxin with his studies of strabismus, and since then the therapeutic areas have exploded. Dr. Andrew Blitzer is the pioneer who first used botulinum neurotoxin to treat focal dystonia of the laryngeal muscles and spasmodic dysphonia. Subsequently, it became clear that botulinum neurotoxin could also block the release of other neurotransmitters, which could be helpful in

autonomic disorders such as hyperhidrosis and pain disorders such as migraine headaches. The therapeutic uses of Botox have extended exponentially to incorporate various medical and surgical conditions. This review evaluates the evidence on Botox used in therapeutic conditions of the head and neck.

MATERIALS AND METHODS

Search strategy and data collection

The PubMed, Cochrane Controlled Trials Register, Medline, and EMBASE databases were searched from 1980 to 2020. The medical subject heading search terms were 'botox' and 'larynx' or 'dystonia' or 'dysphonia' or 'tremor' or 'oral' or 'myoclonus' or 'esophagus or 'temporomandibular' or 'sialorrhoea' or 'bruxism' 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 were identified. Further references were obtained through their bibliographies. Evidence levels, based on those suggested by the Oxford Centre for Evidence-Based Medicine (Table 1), are shown in the text inside [ ].

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

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 ow-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 in the directions and degree of results between individual studies.
b -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 -a cohort study that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), the 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, neck, and face conditions.

Conditions	Highest level of evidence
Laryngeal condition	
Laryngeal dystonia	1a
Stuttering or stammering	4
Vocal tics	2b
Pain	
Headache	1a
Cervical dystonia	1a
Masticatory myalgia	1b
Chronic neck pain	1a
Trigeminal neuralgia	2b
Oral conditions	
Sialorrhoea	1b
Temporomandibular joint disorders	1b
Bruxism	1b
Oromandibular dystonia	4

Facial conditions	
Blepharospasm	1b
Hemifacial spasm	1b
Facial nerve paresis	4
Nasal condition	
Rhinitis	1b
Autonomic conditions	
Frey's syndrome	4

RESULT

The initial search yielded a total of 997 English language studies. After a 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), are shown in the text inside [ ]. The highest level of evidence about Botox treatment for each of the head, neck, and face conditions is presented in Table 2.

DISCUSSION

1. Laryngeal conditions

a. Laryngeal Dystonia-

It is caused by a spasm of intrinsic laryngeal muscles resulting in unseemly closure or opening of the glottis. Its symptoms include hypophonia and breathy voice (abductor type) or hoarseness and strangled speech breaks (adductor type) 3. A meta-analysis of 30 randomized controlled trials 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 It 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

b. Essential voice tremor-

It is characterized by rhythmic activation of mainly the intrinsic laryngeal muscles. The voice is affected by breaks in pitch, diminished fluency, and arrests. Electromyography (EMG)-guided Botox injection into the thyroarytenoid muscles has shown to have a beneficial effect in an RCT (n=13) [1b], 8in a prospective crossover study (n=10) [3b] 9 and a case report [4].10

c. 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 hence, its value in treating this disorder is questionable and requires further research [4].11 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. There is one RCT showing that Botox injections into the thyroarytenoid muscles are efficacious in reducing the frequency and urge of vocal and motor tics(n=18) [2b], however, the patients did not report an overall benefit from the treatment.12Again, further research is mandated to assess the efficacy of Botox for vocal tics.

2. Pain

a. Headache

Numerous multicenter, double-blind placebo-controlled trials support the use of Botox as prophylactic therapy for migraine [1a].13–15 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.1 Significant reduction from baseline was observed in patients in the Botox trial arm about 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, muscle weakness, skin tightness, paresthesia, neck stiffness, and neck pain, can occur at injection sites, but these are minimal and transient.16

b. Cervical dystonia or spasmodic torticollis

This refers to sustained neck muscle contraction resulting in involuntary movements of the head and

neck along with significant cervical pain and abnormal cervical postures. The evidence supporting the use of Botox in the treatment of cervical dystonia consists of 2 Cochrane systematic reviews of 13 (677 participants for Botox A) and 3 (308 participants for Botox B) high-quality RCTs, respectively [1a].17, 18 these meta-analyses showed that a single injection of Botox is effective and can be safely repeated if necessary. After that, 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].19It said that Botox reduces abnormal movements, and contractures and can also prevent secondary degenerative changes of the cervical spine and associated radiculopathy.1

c. Masticatory myalgia

It is a chronic nociceptive irritation of the tendons and fascias of the masseter, temporalis, and medial pterygoid muscles.1 there
Are 3 RCTs
showing Botox to be more effective than placebo (saline)in reducing masticatory myalgia [1b].20-22 The most recent of these 3 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.21 Botox causes disuse atrophy of the affected muscle, which relieves tension, improves aerobic metabolism, and enables decompression of afferent nociceptive neurons through the reduction of substance P-mediated neurogenic inflammation.22

d. Chronic neck pain (no benefit with Botox)

Several studies have assessed the role of intra-muscular Botox injections in chronic neck pain; however, no significant beneficial effect has been demonstrated.

e. 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).23-25All 3 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].23-25Botox was found to be effective in combination with pharmacotherapy, before considering more invasive therapies such as surgery or gamma knife radiosurgery.23

f. 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.26 it is probably due to autonomic dysfunction of salivary myoepithelial cells. Intra-parotid Botox injection was found to significantly decrease symptom severity and improve the patient's QoL in a case series of five patients and a case report [4].27,28

Oesophageal conditions

1. **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 pharyngeal-oesophageal spasms can cause the failure of tracheoesophageal speech and dysphagia.29 traditionally, this was treated with dilation of the pharynx-oesophageal segment (POS), pharyngeal myotomy, and/or oropharyngeal neurectomy.30 more recently, and EMG-guided Botox administration that chemically denervates the cricopharyngeal muscle facilitating tracheoesophageal speech and relieving dysphagia has been reported. There are several prospective31-34 and retrospective outcomes research studies35 assessing the efficacy of Botox using both subjective (videotaped recordings) and objective (video stroboscope) outcome measures [2c]. In corroboration, the most extensive and most recent prospective study consisting of 34 laryngectomies patients showed Botox therapy to be effective in POS voice restoration, especially when combined with speech therapy [2c].34
2. **Dysphagia**
   Incoordination of cricopharyngeal contractions at the initiation of swallowing can result in dysphagia, especially in the elderly population. EMG-guided Botox injections either percutaneously35or endoscopically36to the

cricopharyngeal muscle were found to be effective in the treatment of dysphagia in several prospective and retrospective outcomes research studies [2c].37-41 These results are promising but further, higher-quality studies are needed before the actual value of Botox in dysphagia is determined.

Oral conditions

1. **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].42-44The effects last 3–6 months and can be repeated. Injections can also be used for sialorrhoea caused by salivary fistulas and sialadenitis.45
2. **Temporomandibular joint disorders**
   Spasms of the lateral pterygoid muscles may cause temporomandibular joint (TMJ) disc displacement anteriorly resulting in exquisite pain and clicking. This evidence supporting the use of Botox in the treatment of such TMJ disorders includes multiple RCTs [1b].20, 22 However, injection of Botox into the lateral pterygoid muscle may cause a 'fixed' smile due to diffusion into the superficial facial muscles.45
3. **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. There is one RCT (n=30) that has shown Botox to be efficacious in reducing myofascial pain symptoms in bruxers compared, with control patients receiving saline placebo injections with a second one currently underway[1b].46
4. **Oromandibular dystonia**
   It is a disorder characterized by involuntary, action-induced, tonic, or clonic spasms of the masticatory, lingual and pharyngeal musculature. Symptoms include dysphagia, dysarthria, bruxism and temporomandibular joint subluxation. Case series and case reports are showing favorable effects of Botox injections into the lateral pterygoid, anterior belly of digastric, masseter, and temporalis muscles.47, 48

e. 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 is beneficial in relieving the patient's symptoms [4]. For palatal myoclonus, Botox was injected in the soft palate under EMG guidance,49 while for stapedius myoclonus, Botox was placed transtympanically into the middle ear on a piece of gel foam.50 In the latter case, the beneficial effects of Botox lasted for four months.

Facial conditions

1. **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 1985and it has since become the treatment of choice.1 3 RCTs are demonstrating the superiority of Botox over placebo [1b].50-52

b. **Hemifacial spasm**

This is characterized by unilateral, recurrent, involuntary movements of the muscles innervated by the facial nerve. It occurs due to compression of the facial nerve near its origin by an aberrant branch of the posterior inferior cerebellar artery. The first study to assess Botox in hemifacial spasm was in 1986.53Since then, there have been several studies, including one RCT which showed Botox to be an effective and safe treatment.54This RCT
Involved 11 patients
And demonstrated the beneficial effect of Botox over the placebo [1b].

1. **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 2 case

series of therapeutic chemo-denervation with Botox of these muscles comprising 3 and 10 patients, respectively.55,56Both showed that Botox administration is beneficial in preventing damage as well as healing of the cornea [4]. There is also one case series of 30 patients showing Botox to reduce synkinesis in aberrant facial nerve regeneration following facial nerveparesis.57In that study, Botox was injected into several synkinetic muscles of patients with facial nerve paresis and all 30 patients experienced improvement after treatment [4].

Nasal conditions

1. **Rhinitis**

In an 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].58In another RCT of 20 patients with idiopathic (vasomotor) rhinitis, topical application of Botox on a sponge significantly reduced rhinorrhea compared with placebo (saline) but nasal congestion remained unchanged.59 Middle and inferior turbinate injections of Botox were shown to be a highly effective, safe, and simple intervention in an RCT of 30 patients with vasomotor rhinitis[1b].60 Hence, the role of Botox seems promising in
The treatment of
Allergic and idiopathic rhinitis though several limiting factors prevent its widespread use.

Autonomic conditions

1. **Frey's syndrome**

This typically occurs after parotid surgery and is caused by aberrant regeneration of postganglionic parasympathetic fibers innervating sympathetic cholinergic sweat glands. The result is sweating, flushing, and piloerection while eating (gustatory sweating). Several case series have demonstrated the efficacy of Botox in Frey's syndrome [4].61-63The 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

This literature highlighted the therapeutic role of Botox in a wide range of non-cosmetic conditions about Otorhinolaryngology and Head & Neck Surgery. With ongoing research, the spectrum of clinical applications and the number of people receiving Botox will no doubt increase. Botox appears to justify its title as 'the poison that heals.

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