

Review of Literature**The Role of Botulinum Toxin A in Treatment of Temporomandibular Joint Disorders: A Review**

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ABSTRACT

Temporomandibular joint disorders (TMDs) usually present with symptoms and signs such as pain, mandibular movement, dysfunction, or joint sounds. Botulinum toxin type A (BTX-A) is a biologic toxin which inhibits skeletal muscle through hindering the production of acetylcholine in the nerve endings. This toxin is used for the treatment of hyperactivity of lateral pterygoid muscle and TMD symptoms. This comprehensive review aimed to evaluate the effect of BTX-A injections in the lateral pterygoid muscle on treatment of TMDs symptoms. In this study, online databases including Scopus, Medline, Ebsco, Cochrane, EMBASE, and Google scholar were searched for the keywords "pterygoid muscle" and "Onabotulinumtoxin A". Twenty-four articles were eligible to be enrolled in the study. In 4 interventional studies and 20 descriptive studies, BTX-A was used for the treatment of TMDs. The dosage and number of injections were different in each study; however, the injection methods were relatively similar. Regardless of the type, number of injections, and dosage, injection of BTX-A in lateral pterygoid seems effective in reducing the click sound and other TMJ-related muscle disorders such as pain, hyperactivity, and dysfunction.

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Introduction

There are different signs and symptoms indicating temporomandibular joint disorder (TMD) among which are the temporomandibular joint (TMJ) pain, mandibular movement dysfunction, and joint sounds (click or crepitus). One of the most prevalent findings in TMD patients is articular disc displacement that is the most significant cause of joint click sound. [1-2]

Lateral pterygoid muscle (LP) is one of the four pairs of masticatory muscles. It acts as a fundamental element in horizontal movements of the condyle. [3]

Since this muscle attaches to the joint capsule and possibly the articular disc, [4-5] the relationship between LP dysfunction and TMDs such as anterior displacement of the disc is taken into consideration. [6-7] Accordingly, if changes in normal activities of LP is the main cause of TMDs, treatment of the individual muscle becomes necessary.

Different conservative treatments namely warm compresses, behavioral therapy, oral appliances, and drugs (such as anti-inflammatories and muscle relaxant-s), as well as low-level laser therapy are used to

Table 1: Interventional (experimental) studies

Title of Study	Publication date	Type of study	Control group	Number of patients (n)	Expected result	Result	Score of study with CONSORT checklist
1 Type A botulinum toxin in the treatment of chronic facial pain associated with temporomandibular dysfunction [21]	2001	Interventional (experimental)	Patients before intervention	41	Decreasing painful hyperactivity, Para-function and hyper-mobility	Decreasing the symptoms in 80 % of patients	14
2 Botulinum toxin for the treatment of temporomandibular joint disk disfigurement: Clinical experience [20]	2005	Interventional (experimental)	Patients before intervention	26 Joints [41]	Decreasing pain, dysfunction, click and increasing mouth opening	Positive changing in all cases	18
3 Effect of injection of botulinum toxin on lateral pterygoid muscle used together with the arthroscopy in patients with anterior disk displacement of the temporomandibular joint [22]	2009	Interventional (experimental)	Patients before intervention	43	Decreasing pain, protrusion and left side dislocation	Improvement of symptoms with BTX-A injections in addition to the standard arthroscopy	18
4 Botulinum toxin injection for management of temporomandibular joint clicking [2]	2013	Interventional (experimental)	Patients before intervention	6 Joints [11]	Posterior returning of disk, disappearing click after one week	Significant improvement in disc position	18

treat TMDs. These modalities generally affect all masticatory muscles non-specifically. [8] The interpositional arthroplasty in TMJ-ankylosed patients, using either a temporalis muscle and facial flap or a dermal graft, yielded a comparable and almost satisfactory clinical outcome. [9-10]

Botulinum toxin is the exotoxin of a gram-positive aerobic bacterium called *Clostridium botulinum* with eight different types. [11] Botulinum toxin type A (BTX-A) is a biologic variant that temporarily inhibits the skeletal muscle through hindering the production of acetylcholine and inactivation of calcium channels in the nerve endings. [12] Numerous studies have considered BTX-A injections in LP as a treatment modality. Tintner *et al.* [13] used toxin injections to cure the hyper-tonicity of LP muscles and its consequent bruxism. The use of this toxin in the treatment of joint sounds was reported in 2005 with no recurrence in one-year follow-up period. [14] In another study conducted in 2004, injections of botulinum toxin for patients with articular disc displacement resulted in pain relief and return of the normal movements of the mandible. The treatment was effective and stable up to 6 weeks. [15]

Regarding the fact that pain is the main manifestation and complaint of patients with TMD, it is not surprising that most related review studies have fo-

cused on the effects of botulinum toxin in reducing pain in these patients. The main goal here was a comprehensive review about the impact of BTX-A injections in the LP muscle and treatment of any symptoms of TMDs such as joint sounds, pain, anterior displacement of the articular disc, and mandibular movement disorders in association with LP dysfunction.

Searching Strategy

The selected online databases including Scopus, Medline, Cochrane, EMBASE, and Ebsco were searched for the keywords "pterygoid muscle" and "onabotulinumtoxin A", resulting in 28, 28, 2, 124, and 24 articles, respectively. Finally Google Scholar database was searched which resulted in no new article.

Having eliminated the duplicate articles, 139 articles were obtained in total. Out of these 139, we included those written in English, which were performed, on human between 1984 and 2015 about the BTX-A in lateral pterygoid muscle. Animal studies, those not focusing on the injection in LP, and letters to editor were excluded. Considering the above-mentioned criteria, a total of 28 articles remained.

Three of these articles [8, 16-17] were "narrative review", all the references of which were included in the present study (within the scope of the present study); thus, those three articles were not entailed in

Table 2: Details of interventional (experimental) studies

Title of Study	Site of injection	Type of injection	Injections	Dose	Underlying problem	Side Effects
Type A botulinum toxin in the treatment of chronic facial pain associated with temporomandibular dysfunction	Lateral pterygoid muscle in 8 patients	With electromyography most of the times intraoral	Second injection in 17% of patients	200 units in each side	Painful hyperactivity and hypermobility	Temporary dysphasia and speech disorders in 1 patient
Botulinum toxin for the treatment of temporomandibular joint disk disfigurement: Clinical experience	Lateral pterygoid muscle in all patients	With electromyography at 45° angle	Once	12.5 Units	Disfigurement of TMJ	Temporary dysphasia and speech disorders in 1 patient
Effect of injection of botulinum toxin on lateral pterygoid muscle used together with the arthroscopy in patients with anterior disk displacement of the temporomandibular joint	Lateral pterygoid muscle in all patients	Intraoral with stimulator with 45° angle	Once	20 units	Anterior dislocation of disk	Temporary dystonia in 2 patients
Botulinum toxin injection for management of temporomandibular joint clicking	Lateral pterygoid muscle in all patients	Intraoral with Electromyography	Once	35 units	TMJ click with anterior dislocation of disk without pain and tenderness	Temporary dysphasia and influenza-like symptoms in 1 patient

our review. Another article [18] was excluded, as it was the preliminary report of another article; [19] so we included only the complete report. [19]

The quality of clinical trials was assessed by CONSORT checklist 2010. Accordingly, if the study met any of the CONSORT items, it was scored as 1, and in case of non-compliance, it was scored as 0 for that item; thus the CONSORT score for each study ranged from a minimum of 0 to the maximum of 37 (Table 1).

Data extracted from the 24 articles included the study title, name of the author(s), date of publication, type of the study, the underlying disorders, BTX-A dosage, site of injection, frequency of administration, and treatment outcomes, as well as the possible treatment side effects.

Out of the 24 articles included, 4 were interventional (experimental) studies (Table 1). Generally, all of these studies had reported satisfactory results for the injection of botulinum in the study groups compared with the control groups. Although in some of these studies comparison of some variables between the intervention and the control group had no statistically significant difference, an overall assessment clearly revealed that injection of botulinum toxin in the LP muscle reduced pain, click sound, mandibular deviations in jaw movements, and muscle dysfunction compared with the control group. Table 2 displays more details on the four above-mentioned studies.

Twenty articles were case-report, case series, and retrospective studies as demonstrated in detail in Table 3.

Discussion

Botulinum toxin type A is a paralytic neurotoxin whose main function is to inhibit acetylcholine release at the neuromuscular junction. The U.S. FDA has approved the use of BTX-A in treating blepharospasm, strabismus, hemifacial spasm, cervical dystonia, glabellar lines, and hyperhidrosis. BTX-A is also safely employed in treating hyperfunctional facial lines, other dystonias, spasticity, and head and neck tremor. [8] However, FDA has not firmly approved BTX-A for treatment of masticatory muscles spasm yet, which might be due to the lack of adequate researches on the issue. [3]

Injection of BTX-A in maxillofacial muscles for treatment of pain, tonicity change, and improving the symptoms of TMD has been already considered as a treatment modality by researchers. [13, 16-17] Although, no study has shown the priority of more conservative treatments such as warm and cold compression, splint therapy, physiotherapy, and so on over botulinum injection for the TMD symptoms, conservative methods should be considered as the first treatment line due to the invasiveness of injection. [2, 20]

According to the trend of the current study on the use of botulinum toxin in LP muscle, most researchers

Table 3: Data extracted from Case report, case series, or retrospective types articles

	Title of Study	Publication date/ type of study	Patients (n)	Injection method	Frequency of injections	Dose of injection	Results	Side effects
1	Treating severe bruxism in patients with cerebral palsy with onabotulinumtoxin A [23]	2013	42	With electromyography	1-29 times	50-150 units	+	Mild and rarely
2	Botulinum toxin treatment for upper airway collapse resulting from temporomandibular joint dislocation due to jaw-opening dystonia [24]	2006 Case report	1	With electromyography	3 times	50 units in two sides	+	Mild Dysphasia
3	Treatment of recurrent temporomandibular joint dislocation with intramuscular botulinum toxin injection [25]	2003 Case report	21	With electromyography	1-5 times with 2-6 months interval	50-100 units	+	No side effects
4	Treatment of severe temporomandibular joint clicking with botulinum toxin in the lateral pterygoid muscle in two cases of anterior disc displacement [13]	2005 Case report	2		Twice with 6 months interval	30 units	+	
5	Botulinum toxin injection for the treatment of oromandibular dystonia [26]	1989 Case series	20	With electromyography	Many injections in most of the patients	10-40 units	+	No definite side effects
6	Treatment of recurrent dislocation of the temporomandibular joint with type A botulinum toxin [28]	1997 Case report	1	With electromyography	5	??? units	+	No definite side effects
7	Long-term efficacy of botulinum toxin type A for the treatment of habitual dislocation of the temporomandibular joint [30]	2010 Case report	5	Extraoral	Two extra oral injections	25-50 units	+	No side effects
8	Levodopa-induced peak-dose lateral jaw deviation dystonia [30]	2014 Case report	1	With electromyography	Once	40 units	+	
9	Management of dystonia of the lateral pterygoid muscle with botulinum toxin A [31]	2009 Case report	1	Intraoral	4 times	40-45 units	+	
10	Oromandibular dystonia and hormonal factors: Twelve years follow-up of a case report [32]	2009 Case report	1	With electromyography	3 times	40 units	+ recurrence in pregnancy	
11	Oromandibular dystonia involving the lateral pterygoid muscles: Four cases with different complexity [33]	2007 Case report	4	With electromyography	Each 3- 4 months	25-40 units	+	No significant side effects
12	Somatosensory input and oromandibular dystonia [34]	2013 Case report	2		For the first patient each 3 months, and for the second patient each 5 months	-	+	
13	Medical treatment of recurrent temporomandibular joint dislocation using botulinum toxin A [35]	1997 Case report	1	With electromyography	Once	75 units	+	No side effects
14	Successful treatment of a post-polio tinnitus with type A botulinum toxin [36]	2005 Case report	1	Intraoral, with electromyography	Once	25 units	+	No side effects
15	A comparison of jaw-closing and jaw-opening idiopathic oromandibular dystonia [37]	2006 Case series	12	With electromyography	Once	-	+	
16	Stroke-induced trismus in a pediatric patient: Long-term resolution with botulinum toxin A [38]	2003 Case report	1	Intraoral	2 times for the right muscle and once for the left muscle	15-25 units	+	
17	Jaw-opening oromandibular dystonia secondary to Wilson's Disease treated with botulinum toxin type A [21]	2012 Case report	5	Intraoral, with electromyography	Once	35 units	+	Temporary dysphasia in 3 patients
18	Neurogenic temporomandibular joint dislocation treated with botulinum toxin: report of 4 cases [39]	2010 Case report	4	Electrical Amplifier	Once to twice	25-40 units	+	
19	Treatment of inferior lateral pterygoid muscle dystonia with zolpidem tartrate, botulinum toxin injections, and physical self-regulation procedures: A case report [40]	2004 Case report	1	Extraoral with electromyography	3 times at 4-month intervals	35 units	+	No side effects
20	Lateral pterygoid muscle dystonia. A new technique for treatment with botulinum toxin guided by electromyography and arthroscopy [41]	2011 Case report	1	With electromyography	First time to the inferior head of l lateral pterygoid and second time to the superior head of lateral pterygoid	20 units in each session	+	

confirmed its encouraging results in decreasing the TMD symptoms and muscle dystonia. Based on the physiopathology of the click sounds of TMJ and their

possible association with inappropriate tone of LP in connection with the articular disc, [4-7] undoubtedly, relaxation and normal muscle tone can reduce the

symptoms. [2, 20] Details of botulinum toxin injection in LP muscle in qualified extracted articles are listed in Table 2.

For many years, BTX-A has been used to treat the hyperactivity of LP muscle. [13] Rao *et al.* conducted a review and pointed out the results of several clinical trials and case reports which had endorsed various uses of BTX-A in maxillofacial area including in dental implants surgeries, gummy smile correction, muscle hypertrophy and spasms, headaches (such as migraine), and trigeminal neuralgia, as well as the role of botulinum toxin injection in the masseter muscle for the treatment of TMD. They noted that although toxin might decrease the muscle strength and mastication force, it would be temporary and the normal function would return when the effect of toxin vanished. [16]

In an evidence-based review, Ihde *et al.* [17] evaluated the therapeutic effect of botulinum on relieving chronic facial pain. They noticed adverse effects such as muscle paralysis and dysphagia in a number of patients. It was described as the temporary symptom, and recovered after a short time. They also pointed out that four weeks after beginning the treatment, about 91% of patients expressed improvement in facial pain. [17]

Song *et al.* [8] investigated the effects of botulinum toxin on the treatment of TMD. They aimed to collect and define a specific algorithm for treatment of TMD patients. They announced that conservative treatments such as warm compresses, behavioral therapy, oral appliances, and drugs (like anti-inflammatories and muscle relaxants) were prior to BTX-A injection. [8] Hence, toxin was recommended for patients who would not respond to conservative treatments. They also deduced a recommended dose of BTX-A in treatment of TMD patients, which was 7.5-10 of the standard unit for LP muscle, prescribed in case of sub-maxillary pain, jaw deviation, or habits such as bruxism. [8]

Emara *et al.* [2] assessed the effects of botulinum toxin in LP muscle for the treatment of joint click in 6 patients (11 involved joints). The electromyogram (EMG) was used to define the proper insertion site of injection. They observed that toxin injection eliminated the click sound in 10 joints during the first week and in one joint after a week. During three to four following months, recurrence of click sound was reported

in only one joint. [2]

Later, von Lindren [21] evaluated the effect of botulinum toxin injections on reducing the maxillofacial muscle pain associated with TMJ dysfunction. EMG was employed during injection in muscles that were difficult to access including the lateral pterygoid muscle (8 out of 41 patients). Accordingly, localized pain was recovered in 80% of patients and remained in about half of the patients for 3 months after injection. [21]

The injection method

Due to the more difficult access to LP muscle compared with other masticatory muscles, EMG was used to determine the exact place of needle entrance. According to EMG guidance to LP, the needle may insert extra-orally anterior to the condylar neck with 45° angle. In cases of intra-oral access, the injection site would be posterior to the maxillary tuberosity with 45° angle. [2, 18-19]

Frequency of injections

In three of the experimental studies [2, 20, 22] a single injection was administered; and in one study, [21] 17% of patients received a second injection. Generally in these studies, the impact of single dose normally last until the end of the follow-up period. In all investigated cases, the first dose yielded relatively favorable outcomes and repeated doses after 2-6 months were performed to strengthen the effect of previous injection. The frequency of booster dose injection varied among the reported cases (Table 3).

Dose of injection

In the experimental studies, [2, 20-22] a dose of 12.5 to 200 units per muscle was used. Different case reports mentioned various injection doses (Table 3). With respect to the desired treatment outcome and lack of comparison with other studies, the administered dose and any definitive guideline which was used were not challenged. In an overview, it seems that researchers used proper doses of injection based on the severity of involvement; for instance, the maximum dose (150 units per muscle) was used for bruxism subsequent to cerebral palsy, [23] airway collapse caused by jaw dislocation associated with muscle dystonia, [24] and recurrent dislocation of the jaw. [25]

Adverse effects of injection

The previously reported adverse effects such as belph-

aroptosis, brow ptosis, and diplopia at the site of injection which were seen in the treatment of headache disorders were not matters of issue in the present research. [26] In the experimental studies, [2, 20-22] the side effects of injection were often mild or transient and were reported in quite a few percent of the patients. The majority of these studies reported only temporary unwanted symptoms such as dysphagia, difficulty in articulation, muscle weakness, transient speech disorder, and flu-like symptoms. [8] In other reviewed articles, no side effect was observed except for the temporary mild dysphagia (Table 3). There were also minor complications associated with needle injections such as bruising and local tenderness. [8]

Since none of the interventional studies reported any evidence to avoid the toxin injection in the maxillofacial muscles, the temporary problems may not be a contraindication to the use of this toxin as a treatment modality for TMD.

Conclusion

Injection of BTX-A in LP muscle, considering the different methods, frequencies and injection dosages used in different studies, would decrease the clicks and other TMJ-related disorders such as pain, hyperactivity, and dysfunction. Based on the present review, the majority of studies about the injection of botulinum toxin in LP muscle reported cases or were done as quasi-experimental studies. Hence, clinical trials and single-blind or double-blind studies assessing the effect of the toxin in LP muscle seems necessary.

Conflict of Interest

The authors of this manuscript certify no financial or other competing interest regarding this article.

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