The Effects of Botulinum Toxin-A Injection on Lateral Pterygoid Muscle in Patients with Painful Temporomandibular Joint Click: A Randomized Clinical Trial Study

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Research Article

Keywords: lateral pterygoid muscle, temporomandibular disorders, botulinum toxin, temporomandibular joint, orofacial pain

Posted Date: July 27th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-640270/v1>

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Abstract

Background: The aim of this study was to investigate the effect of Botulinum toxin-A (BTX-A) injection in lateral pterygoid (LP) muscle and analyze the efficacy of this treatment modality in reducing Temporomandibular disorder (TMD) symptoms. TMD is the main cause of nondental pain in the orofacial area. The most common symptoms of temporomandibular disorder are joints pain and sound and limitation of jaw function. Botulinum toxin (BTX) injection in LP temporarily paralyses the muscle. BTX injection is considered as a potential treatment for TMD, due to its pain relieving characteristic and its ability to reduce muscle activity. However, these evidences are mostly case series and more studies are required to prove its efficacy.

Methods: Thirty-eight patients (19 women and 19 men, mean age: 26.53 years) with painful unilateral temporomandibular joint click and LP muscle tenderness entered the study. They were divided into two groups; one received extraoral Botax injection in LP muscle, and the other was injected by placebo. Pain severity, jaw's range of movement, click severity and Helkimo-Index, were taken recorded at first and also in follow up in first visit and in one week, one month and three months after intervention. Data were analyzed using Repeated measures ANOVA and t-test.

Results: The result showed that click severity was not significantly different between BTX and placebo groups ($p=0.07$). Pain and Helkimo index were decreased significantly in BTX group ($p=0.00$ and $P=0.006$ respectively); however, there was no significant difference when compared between the two groups ($P=0.22$ and $p=1$ respectively). There was a significant difference in lateral movements between the groups ($p=0.00$) but not in protrusion movement ($p=0.095$).

Conclusions: It can be concluded that although some studies state that BTX injection can make the click sound disappear, in this study we did not find a significant difference between two groups. Furthermore, our results showed that click and pain severity were decreased, but the difference was not statistically significant. Therefore, further studies with more dosage of BTX and higher participants seem to be necessary.

Trial registration: The local Ethics Committee of Shiraz University of Medical Science approved this research under Ethics code: IR.SUMS.REC. 2018/10/01 and IRCT number: IRCT20130521013406N3.

Background:

TMD, usually known as chronic orofacial pain, are a group of musculoskeletal diseases which can involve masticatory muscles, temporomandibular joint (TMJ) and the associated structures (1). It is divided into two categories, intra-articular or extra-articular (2). In more than 50% of patients, Musculoskeletal problem is the main cause (3). The most prevalent cause for intra-articular TMD is articular disc displacement which involves condyle-disk relationship (4).

TMD is currently considered a multifactorial disease, but it could be due to biological, psychosocial or structural dysfunctions (5). TMD usually accompanies anatomical, functional and histological irregularities in Musculo-articular structures which is followed by various clinical findings such as temporomandibular joint pain, sounds of joint and limitation of jaw function (6). One of the most common types of TMDs is disk displacement as an internal derangement of the TMJ (7). It may result in decreasing articular space, joint sounds (clicking, popping or crepitation), arthritis, condylar resorption, jaw deformities and pressure on the retro discal tissue, which can itself has a role in inducing pain and dysfunction (8).

Although TMD is the main cause of nondental pain in the orofacial area, only 5% of affected adults seek treatment (9). The most routine non-surgical treatments are: physical therapy, oral appliances, pharmacotherapy and low-level laser therapy (LLLT) ; which generally affect all masticatory muscles rather than a specific one (10).

As generally agreed, conservative treatments should always be the first choice for TMDs. Painful joint sound (click) is a common complain of patients (11).

Disc displacement with reduction (DDWR) is clinically characterized by reciprocal click. According to a study by Ziegler et al, routine treatment regimen is consisted of education, exercises, appliances, LLLT and in some cases arthroscopy. However, clicking has not decreased significantly (12). For treating DDWR, anterior repositioning splint was also suggested in order to maintain the normal relationship between disc and condyle (13).

Botulinum toxin (BTX) is synthesized by a gram-positive, anaerobic bacterium called *Clostridium botulinum* (14, 15). Botulinum toxin type A (BTX- A) is a biologic type that paralyses the muscle temporarily by delaying the acetylcholine production and inactivating the calcium channels in the nerve terminations (12). According to available clinical reviews, BTX has been considered as a potential treatment for TMD, due to its pain relieving characteristic and its ability to reduce muscle activity. (10, 16, 17) BTX has been used extensively in treating hemifacial spasm, oromandibular dystonia, spasmodic dysphonia and recently TMDs (18).

Lateral pterygoid (LP) is a two headed muscle which plays a major role in mastication and horizontal movements of the mandible (19). This muscle attaches directly to articular disc and joint capsule (20, 21), therefore TMDs are greatly related to anterior disk displacement (22). Consequently, treatment of LP muscle dysfunction is essential in TMDs followed by LP abnormalities.

Some authors have found positive effects by injecting BTX in LP muscle which decreased TMD symptoms, however they are mostly case reports (7, 23–25). Emara et al have reported a significant improvement in disc position and elimination of joint sound after injection of BTX in LP muscle (7). In another study conducted in 2005, after Injection of BTX-A in LP, clicking has been permanently eliminated and disc-condyle relationship has been improved (25).

The aim of this study was to investigate the effect of BTX-A injection in the LP muscle and analyze the efficacy of this treatment modality in reducing or elimination of TMD symptoms such as pain, clicking sound, disc placement, and mandibular movements. So, we compared the effect of extra oral BTX-A injection with normal saline in LP muscle, in patients with painful click, through a randomized clinical trial (RCT). This study adheres to CONSORT guidelines.

Methods:

In this double-blind randomized clinical trial study, all methods were carried out in accordance with relevant guidelines and regulations and all experimental protocols were approved by the local Ethics Committee of Shiraz University of Medical Science under ethics code: IR.SUMS.REC.1397/07/09 and the IRCT number: IRCT20130521013406N3. Informed consent was obtained from all subjects.

We selected 38 patients who had referred to Shiraz Dental Faculty, Oral and Maxillofacial Disease Department. 19 women and 19 men were included (with mean age of 26.53 years), however two men refused to continue collaboration. All patients had painful unilateral TMJ click with lateral pterygoid muscle tenderness, while other muscles were normal. A Panoramic radiography (OPG) was ordered before intervention to rule out cysts or bony abnormalities in TMJ.

A complete clinical and medical examination was done to exclude candidates suffering from neuromuscular disorders, musculoskeletal disorders, joint disorders (bone deformities, inflammatory, septic, etc), jaw fractures, parafunctional habits or malocclusion. Patients were randomly entered into two groups by block randomization (26); 18 patients in experimental (BTX) and 18 in control (placebo) group. All patients who were older than 18 years old, were informed about the planned treatment and signed a detailed and complete written consent explaining them that they might receive a Botax injection or a placebo; while knowing that they all would receive the conventional pharmacotherapy prior to the study. All patients were treated with Naproxen 250 mg (q 12 h) and Methocarbamol 500 mg (q 8 h) for two weeks, in order to alleviate the pain before any intervention starts.

This study was approved by the local Ethics Committee of Shiraz University of Medical Science (ethics code = IR.SUMS.REC.1397/07/09) and the IRCT number is IRCT20130521013406N3.

Clinical findings such as: pain severity, jaw movements, click severity and Helkimo-Index (for TMD evaluation), were recorded in first visit and in one week, one month and three months after intervention.

TMJ pain severity was evaluated according to the visual analogue scale (VAS) (27). We also measured maximal inter-incisal opening (MIO), the range of lateral movement and protrusion of jaw by a calibrated coulis (Insize, China), recorded in millimeters (mm).

Click severity was assessed according to the following criterion; 0 = no sound, 1 = little sound (could not be heard without stethoscope), 2 = loud sound (could be heard without stethoscope).

Patients in experimental group, received BTX-A extraoral injection in LP muscle, in clicking side.

BTX-A vial was reconstituted by 2 ml of 0.9% normal saline to prepare a 15 U/0.1 ml solution (Dysport 300 U powder for injection); Clostridium botulinum type A neurotoxin complex, Dysport, Ipsen from Mulholland LtdUK); 0.1 ml of this solution containing 15 U BTX-A was used for injection with dentistry syringe; We used Kai-Yuan Fua method (28) for injection. The LP muscle was approached extraorally. Syringe was inserted anterior to the condylar neck with 45° angle, 1 cm below the central zygomatic arch and 0.5–1 cm anterior to the condyle of the mandible (Fig. 1). Aspiration was carried out to avoid unintentional intravascular injection, since the muscle is surrounded by pterygoid venous plexus.

We followed patients 1 week, 1 month and 3 months after and measurements were recorded again. For the control group (placebo), we injected normal saline with the same volume and in the same area.

The sample size was designed based on statistical analysis. Data was analyzed using SPSS version 22 (SPSS Inc., IL, USA), applying mean $\pm$ standard deviation and frequency (%). Paired t-test was applied to compare all data such as age, pain and Helkimo index prior to study. T-test was employed in order to compare the mean differences in Helkimo index and VAS. Repeated measures ANOVA (RM-ANOVA) was used to assess the changes in pain scores within study groups. In all our analysis, results were considered statistically meaningful in case the p-value was equal to or lower than 0.05.

Results:

Out of thirty-eight patients, two men refused to continue collaboration, therefore 18 candidates in BTX and 18 in placebo group completed all treatment sessions. Mean age of patients was 26.53 years old (28.28 ± 7.9) in BTX group and 24.78 ± 4.5 in placebo group). Mean age, pain severity (VAS) and Helkimo index in two groups were not significantly different according to the t-test prior to intervention ($p=0.11$, $p=0.13$, $p=0.37$, respectively). Regarding Chi-square test both groups were similar in gender distribution ($P=0.5$) (Table 1).

Table 1
Demographic information of experimental and control groups

group	Number	female	male	Mean age (year)
Experimental (BTX)	18	11	7	28.78
Control (placebo)	18	8	10	24.78

In both BTX and placebo groups, significant decrease was found in click severity considering follow up visit in 1 month after injection ($P=0.05$, $p=0.001$ respectively). However, in month 3, the click severity has decreased in BTX group ($p=0.06$) and in placebo group it was increased ($p=0.137$); but the difference was not statistically significant ($p=0.07$) (Table 2).

Table 2
Means of variables in BTX-A and placebo (normal saline) groups in different time

Group	Time	Click*	VAS	Maximum opening (mm)	Lateral movement (mm)	Protrusion movement (mm)	Helkimo INDEX
BTX-A	baseline	2.00	4.72	43.45	8.28	7.46	7.77
	1week		2.11	43.89	8.15	7.58	
	1month	1.05	1.78	43.86	8.15	8.21	3.5
	3month	1.07	2.00	43.66	8.54	7.49	3.38
Placebo	Baseline	2.00	3.50	49.82	9.01	6.83	6.56
	1week		1.78	47.27	8.54	6.40	
	1month	1.11	1.72	46.63	8.08	6.26	2.86
	3month	1.52	1.89	46.11	7.55	5.98	4.61
* Click: 0 = no sound, 1 = little sound (could not be heard without stethoscope), 2 = loud sound (could be heard without stethoscope)							

The effect of BTX injection on pain severity was evaluated by Repeated Measure-ANOVA model. Pain was decreased significantly after 1 week and lasting for 3 months after BTX injection ($p = 0.00$); (Fig. 2)

Comparing BTX and placebo groups, there was no significant difference based on pain severity during all follow up period ($P = 0.22$). Hence, both groups had a similar trend in pain relief.

According to t-test, Helkimo index was significantly decreased after 1 month and 3 months in BTX group ($P = 0.000$, $p = 0.000$ respectively); however, there was no significant difference between these two times based on Helkimo index ($p = 0.99$). In placebo group, Helkimo index was significantly decreased after 1 month ($p = 0.000$); but after 3 months, Helkimo index was significantly increased in comparison with the first month ($p = 0.002$). Besides, there was no significant difference between BTX and placebo groups based on Helkimo index at the end of three months ($p = 0.18$).

When assessing jaw movements in BTX group, the maximum opening was not significantly changed in follow up visits ($P = 0.17$) and there was no difference between placebo and BTX group ($P = 0.08$). There was a significant difference in lateral movements between two groups ($p = 0.00$). The lateral movement in BTX group had gradually increased during 3months follow up, but it was not statistically significant ($p = 0.59$). In contrast, placebo group's mean of lateral movement decreased by the time (especially after 3 months in comparison with base line, $P = 0.02$) (Fig. 3).

There was no significant difference in lateral movement between two groups in different session (1week, 1month, 3month, $p = 0.12$, $p = 0.52$ $p = 0.17$, respectively). There was a significant difference in changes of protrusion movement amongst two groups ($p = 0.00$). The protrusion movement in BTX group had gradually increased, especially during the first month, but returned to base line after 3 months; however,

these changes were not statistically significant ($p = 0.23$). In the placebo group protrusion movement had gradually decreased during 3 months, but it was not significant ($p = 0.66$) (Fig. 4).

Generally, there was no significant difference in protrusion movement between groups during follow up sessions ($p = 0.095$).

Discussion:

To the best of author's knowledge, there are only few similar studies that have evaluated the effects of BTX-A injection on click severity and these studies were mostly limited to case series. (24). The present study was designed according to the promising preliminary results of Bakke et al.(8) and Emara et al. (7)

They reported successful use of BTX-A injection as a treatment for TMJ clicking, however these studies were case reports and case series. On the other hand, our study was designed as a randomized clinical trial and we compared the effects of BTX-A injection on TMD with normal saline.

Results showed that although BTX-A decreased the click severity in 3 months in compare to the placebo group, there was no significant difference in resolving click between the two groups. It was also seen that both BTX and normal saline injection had reduced the click sound in 1 month; but in month 3 there was a decrease in click severity only in BTX group (however not significant) which can possibly indicate the effectiveness of BTX in our study.

It is also notable that maximum opening and lateral and protrusive movements have been increased in BTX-A group, when comparing results in month 3 with baseline; however, the differences were not statistically significant (Table 2).

The difference between our results and other similar studies (7, 8) could be due to several reasons. First, those studies were case series and did not compare the result with placebo. It could also be due to different methods, amount (BTX dosage) and frequency of injections. These studies used intra oral route for access to lateral pterygoid muscle, but we used extra oral method based on Kai-Yuan Fu study (28). Volume of injection was also lower than other studies due to the probable risk of hemorrhage as a result of proximity to the maxillary artery and the pterygoid venous plexus. The other cause of this insignificant result might be unilateral injection. It should also be mentioned that as mean age of BTX-A group was 4 years younger than control group (Table 1); it can be expected that in control group, the problem diminishes as self-limit in comparison with BTX-A group. Above all, larger sample size can result in more specific results.

Based on the present study, pain severity (VAS) was reduced significantly after one week following the injection. The mean VAS in BTX group was lower than in the placebo group, but it was not significantly different. Normal saline may wash joint space and decrease inflammatory mediators and act as joint lavage. Similar to our results, kurtoglu (29) Emara and bakke (7, 8) reported that pain was decreased and psychological statues improved during the time. On the other hand, psychological effects might have an

impact on our results (the so-called placebo effect). This might confirm that despite decreasing click sound during the first week, it returns after one month in the placebo group. Overall, patients were satisfied with the treatment, especially during the first month. It should also be noted that all patients had received medicine (NSAIDs and muscle relaxants) for two weeks before intervention, and were trained to follow approaches such as eating soft foods and chew bilaterally, using warm pack etc.; hence it can itself have a role in decreasing the symptoms in both groups.

In VON Lindern study 200U BTX was used for all masticatory muscle such as masseter, temporalis and lateral pterygoid for treatment of painful hyperactivity, parafunctions and hypermobility of jaw and result were satisfactory due to pain reduction (30). Muscles act as a team and relaxation in all of them results in noticeable decrease of pain. Also Karacalar (31) used BTX in both medial and lateral pterygoid muscle and good result have been obtained, use of this two muscle as a one unit might be better to release pain faster. Though, we aimed to paralysis only the lateral pterygoid because of its role in anterior disk displacement (click) due to its attachment to the disc.

Dosage of BTX for injection varied in different studies, which depends on muscle bulk and site of injection. For masticatory muscles (temporalis and masseter) the recommended amount of BTX for each muscle ranges from 40 to 60 U each at several injection points (29). Since the lateral pterygoid is a small muscle and located deeply and adjacent to several vital structures that may be affected by seepage, it requires a lower amount and the injection is made at a single point. In some studies (7, 8), 35 U was injected intraoral and other researcher had used 50 U in the lateral pterygoid, but this was accompanied by a higher percentage of side effects such as dysphagia (32). We selected 15 units BTX for injection in lateral pterygoid.

We implemented the extra oral approach like Fu KY and Ziegler CM in our study (12, 28) because the access for injection was more comfortable than intraoral injection. 15U was injected in the lateral pterygoid and patients were followed up as mentioned in the method section. Based on our result; it seems intraoral approach may have better results for paralysis of lateral pterygoid in treating clicking.

Similar to other studies, maximum jaw opening did not change (7, 8), but mean of lateral movement and protrusion increased gradually in BTX group. Lateral pterygoid relaxation is a cause that patients can move their jaw more comfortably without pain, although statistically was not different with the placebo group.

The initial diagnosis of click was obtained by clinical examination and complains of patients, and based on American Academy of Orofacial pain criteria. One of the benefits of present study, was the using of different measurements such as helkimo index, VAS and all of movement separately for better evaluation. Helkimo-index was measured before and after treatment and it was a positive point, previous researches did not measure it. This index was used to roll out the psychology effects. (hajian 2016) TMJ series radiography also was obtained and pathologic problems were excluded from the study.

In this study we had some limitation, it was better to evaluate disk position before and after treatment with MRI because it shows the disk position better and can detect it more properly. Electromyography is a useful devise that can be used with injection to assure that needle enters into muscle properly and not into space. In this study, like alveolar nerve block injection, we used anatomic points.

Conclusion:

Injection of BTX-A in masticatory muscles for treatment of TMD is used routinely, but there are not adequate studies on click specifically; hence, we performed this method as RCT. It is also assumed that BTX could be considered as an appropriate substitute for corticosteroid injections in treating TMD, especially in patients who are contraindicated to receive corticosteroids due to some special conditions such as: osteoporosis, uncontrolled hyperglycemia, diabetes mellitus etc. Our results showed that click and VAS were decreased after BTX injection, but the difference with control group was not statistically significant. Therefore, further studies with more dosage of BTX and higher participants seem to be helpful.

Abbreviations

Abbreviation	Meaning
BTX-A	Botulinum toxin-A
LP	lateral pterygoid
TMD	Temporomandibular disorder
BTX	Botulinum toxin
TMJ	Temporomandibular joint
LLL	low-level laser therapy
DDWR	Disc displacement with reduction
RCT	Randomized clinical trial
VAS	Visual analogue scale
MIO	Maximal inter-incisal opening
mm	Millimeters

Declarations

Ethics approval and consent to participate:

The local Ethics Committee of Shiraz University of Medical Science approved this research (ethics code=IR.SUMS.REC.1397/079) and the IRCT number is IRCT20130521013406N3.

All patients were informed about the planned treatment and signed a detailed and complete written consent explaining them that they might receive a Botax injection or a placebo; while knowing that they all would receive the conventional pharmacotherapy prior to the study.

Consent for publication:

We, all authors, give our consent that all details, which include photographs, figures and all other materials within the text, to be published in the BMD Journal. Besides, written consent to publish any personal and clinical details is obtained from all participants.

Availability of data and materials:

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

This research was funded by shiraz university of medical sciences. The role of funder was only limited to supporting the costs of materials and any other financial issue relating to the study.

Authors' contributions:

FR: Study design and concept, data interpretation, drafting, Final approval, agreement to be accountable for all aspects of the work.

NE: Study design and concept, data collection, drafting, Final approval, agreement to be accountable for all aspects of the work.

AA: Data interpretation, drafting, Final approval, agreement to be accountable for all aspects of the work.

SE: Data interpretation, drafting, Final approval and was a major contributor in writing the manuscript, agreement to be accountable for all aspects of the work.

Acknowledgement:

The authors would like to thank the Vice-Chancellery of research, Shiraz University of Medical Sciences, for supporting this research (Grant #16144). This article is based on the thesis by Dr. Negin Esnaashari. The authors want to thank Dr. Reza Dehghani for conducting the Botox injections. The authors would like to also thank Dr. Mehrdad Vosoughi, master of the Dental Research Development Center, School of Dentistry, for his help with the statistical analyses. The authors wish to thank Mr. H. Argasi at the Research Consultation Center (RCC) of Shiraz University of Medical Sciences for his invaluable assistance in English editing of this manuscript.

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Figures

BTX injection:

Normal saline injection:

Figure 1

site of injection:

Figure 2

Comparing pain severity (VAS) between Botax (BTX-A) and normal (normal saline) groups.

Figure 3

Comparing lateral movement between Botax (BTX-A) and normal (normal saline) groups.

Figure 4

Comparing protrusion movement between Botax (BTX-A) and normal (normal saline) groups.