Efficacy of botulinum toxin therapy in treatment of myofascial pain

Jorge Chaurand1), Laura Pacheco-Ruíz1), Hector Orozco-Saldívar1), and Julio López-Valdés2)

1)Maxillofacial Surgery Department, National Medical Center “20 de Noviembre” ISSSTE, Mexico City, Mexico
2)Medical Direction of Teaching and Investigation, ISSSTE, Mexico City, Mexico

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Abstract: The present study aimed to assess the efficacy of using botulinum toxin (BTX) in temporomandibular joint disorders, particularly pertaining to myofascial pain from masseter and temporal muscles. The study included 11 patients who were diagnosed with masseter and temporalis myofascial pain. Visual analog scale for pain and pressure algometry were conducted initially, after 1 month of conservative therapy (control group), and after 1 month of BTX type A injections (study group). Data were statistically analyzed (analysis of variance and Wilcoxon’s test) to determine intergroup differences. Both conservative therapy and BTX injections showed reduction in pain scores and increase in pain threshold compared with baseline, and statistically significant differences were noted between both groups. Thus, BTX injections appear to be effective in management of chronic myofascial pain targeting masseter and temporalis muscles.

Keywords: botulinum toxin; temporomandibular joint disorders; myofascial pain.

Introduction

Masticatory myofascial pain is a common cause of chronic facial pain, characterized as chronic focal muscular pain possibly with locking and restricted mouth opening. Affected patients may also have headache or cervical pain if frontalis or cervical muscles are involved (1). The clinical sign of myofascial pain is the presence of a trigger point; this contains a sensory component of sensitized nociceptors that produce sensations of pain, localized twitching of muscles, and referred pain (2,3). The motor component of myofascial pain is caused by excessive acetylcholine (Ach) discharge from multiple dysfunctional endplates that causes contraction knots to accumulate in muscle fibers and a palpable band of taut muscle, which is pathognomonic of trigger points in the condition (4,5).

Botulinum injections can improve blood flow to the muscles and release the nerve fibers compressed by abnormally contracting muscles, both of which may contribute to the cause of pain (6). In addition, botulinum injections can have an immediate effect owing to direct release of endogenous endorphins from introduction of the needle and alteration in the balance of central neurotransmitters; this is caused by local inhibition of pain peptides from sensory ganglions and nerve terminals, and anti-inflammatory and antiglutaminergic actions (7,8). Moreover, studies have shown that 3-10% of patients develop neutralizing antibodies with long-term adverse effects that include muscular atrophy (9).

According to the American Academy of Orofacial Pain, temporomandibular joint disorders (TMDs) are...
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classified into two groups: myogenous TMD, which is related more to masticatory muscle disorders, and artrogenous TMD, which is related more to the temporomandibular joint (TMJ) itself (10). On the other hand, the research diagnostic criteria (RDC) categorizes TMDs into three groups according to the common factors among conditions: group I is myofascial TMD, group II is disc displacement, and group III includes other TMDs such as arthralgia, osteoarthritis, and osteoarthrosis (11).

A recent meta-analysis of epidemiology of Axis I (TMD based on physical diagnosis) revealed that myofascial pain affects almost half of the patients presenting for TMD treatment. Despite the widespread prevalence of myofascial pain disorders, no definitive treatment approaches have been established (12).

Various treatment modalities have been suggested for TMD, from patient education, pharmacological therapy, and psychological therapy as well as noninvasive interventions such as physiotherapy and splints to further surgical interventions. Botulinum toxin (BTX) is a potent neurotoxin synthesized by the Gram-negative, anaerobic, spore-forming bacterium Clostridium botulinum. It blocks presynaptic release of Ach into the end plate of the neural junction, thus leading to reduced activity of muscles or glands (13). Until recently, increasing research has suggested independent actions of BTX on peripheral nociceptors by blocking release of neurotransmitters, including pain and inflammatory mediators. Owing to its ability to reduce muscle activity and pain-relieving effects, BTX has gained popularity as a potential therapy for TMD, with available clinical reviews supporting its benefits (14).

The aim of this self-controlled preliminary trial was to assess the efficacy of BTX in TMD management, particularly for myofascial pain from masseter and temporal muscles, by means of pressure algometry and visual analog scale (VAS).

**Materials and Methods**

This study was conducted between August 2014 and December 2015 (Table 1). Subjects included adults who were clinically diagnosed with bilateral myofascial pain caused by hyperactivity of masticatory muscles, parafunctional movement, and hypermobility according to RDC/TMD. Patients with conditions other than TMDs, such as TMJ dislocation, congenital or developmental disorders, systemic inflammatory connective tissue diseases (e.g., rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis), myasthenia gravis, Lambert-Eaton syndrome, fracture, or neoplasia, were excluded. All patients underwent 3-stage measurements as part of the trial (baseline, conservative therapy, and BTX injection) by primary researchers Chaurand J. and Pacheco L. (both with considerable expertise of 10 and 25 years in TMJ diagnosis and treatment), who were aware of the stage for each patient. This study followed the Declaration of Helsinki and the regional Ethical Review Board of the National Medical Center “20 de Noviembre” ISSSTE approved the study (370.2015). All participants provided written informed consent.

**Baseline data recordings**

All patients underwent clinical examination consisting of mandibular movement capacity (range opening [mm]), pain on palpation of TMJ muscles, joint pain on movement, and presence of joint sounds. During the first visit, trigger points in masseter (superior and inferior) and temporalis muscles were localized by physical examination.

Subsequently, VAS scores for identified trigger points were recorded with pressure algometry (objective outcome) at the time of diagnosis (subjective outcome).

Table 1 Demographic characteristics of the study population

<table>
<thead>
<tr>
<th>No.</th>
<th>ID</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Baseline VAS (mean ± SD)</th>
<th>Baseline pressure algometry (mean ± SD)</th>
</tr>
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<tr>
<td>1</td>
<td>MIME</td>
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<td>8.66 ± 0.516</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<td>14.75 ± 2.32</td>
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<tr>
<td>4</td>
<td>GFAT</td>
<td>52</td>
<td>Female</td>
<td>9.67 ± 0.516</td>
<td>11.16 ± 2.14</td>
</tr>
<tr>
<td>5</td>
<td>TRE</td>
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<td>6</td>
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<tr>
<td>7</td>
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<tr>
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<tr>
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<tr>
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</tr>
<tr>
<td>Total</td>
<td></td>
<td>Mean 49.18 ± 8.9 (SD)</td>
<td></td>
<td>8.48 ± 0.575</td>
<td>12.95 ± 2.08</td>
</tr>
</tbody>
</table>
An analogous pressure algometer (baseline push pull) was used for evaluation of muscle tenderness of selected components in the masticatory motor system, such as superficial and deep parts of the masseter muscle and anterior and/or posterior parts of the temporalis muscle. All examinations of the aforementioned muscles were performed extraorally. The algometer consisted of casing, slide, and steel spring. A precision scale on the cover allowed for assessing the force. The slider in the shape of piston had a circular footplate (area size: 1 cm²). Accuracy of the algometer was 0.5 N. Algometric measurements were performed by a single examiner alternatively on the right and left sides, with constant sequence of examined structures. There was an interval of 5 s between examination of the right and left sides. Examination was performed with the patients' dental arches in a slightly open position and the muscles relaxed. During examination, the footplate of the algometer was always held perpendicular to the skin, in the trigger point of the examined muscle, applying constant force until the patient reports pain (pain threshold). All patients had reported a certain degree of pain targeted in both masseter and temporalis muscles for at least 6 months before consultation.

**Conservative therapy data recordings**

After baseline evaluation, a month of conservative treatments was prescribed for all patients: i) massage, ii) relaxing technique, iii) heat packs, iv) soft diet, and v) Celecoxib 100 mg (Pfizer, New York, USA) as necessary. No splints, muscle relaxants, tricyclic antidepressants, or others drugs were used in any of the patients.

After a month of conservative treatment, pressure algometry (at same bilateral muscle sites) and VAS scoring were conducted again. Thereafter, patients received BTX injections for further comparison between groups.

**Botulinum toxin injections**

Preparation of drugs and syringes was performed by a research assistant: the BTX solution was prepared by dissolving 100 IU BTX (Xeomeen, Merz Pharma, Frankfurt, Germany) into 1.0 mL of sterile saline solution (0.9%) at room temperature. This was performed immediately before injection; a 1-mL insulin syringe with a hypodermic needle was used for injections.

In total, 60 Units (1U) were injected bilaterally (three trigger points on each side) per patient in a single session by both main researchers: 10 U at the lower masseter (near the mandibular angle), 10 U at the upper masseter (near the zygomatic arch), and 10 U at the temporalis muscles according to trigger point localization (Fig. 1). Conservative therapy was withdrawn, and a month later, the same measurements (as baseline and conservative therapy) were recorded (VAS and algometry).

**Statistical analyses**

Overall, 11 Hispanic females with mean age of 49.2 ± 8.9 (range, 36-60) years completed the study with baseline, conservative therapy data recordings, BTX injections, and final measurements. Data are reported as absolute numbers, percentage of the whole sample, or mean ± standard deviation (SD). Intergroup differences among particular groups were analyzed using analysis of variance (ANOVA) (algometry) and Wilcoxon’s test (VAS). In addition, chi-squared test ($\chi^2$) was performed for the calculation of range opening. All results were considered significant at a $P$ value less than 0.01. All efforts were made to eliminate potential sources of bias.

**Results**

**Pain evaluation**

After a month of management with both treatments (conservative therapy and BTX injection), decrease in pain intensity was assessed using two techniques: VAS scores and algometry. A change in pain threshold was noted based on algometer scores (Fig. 2). Of the 11 patients who received conservative therapy, an overall increase in pain threshold, 6.6% of the baseline value, was observed ($\mu = +0.86$ pounds ± 0.795 SD). Nevertheless, 4 (36.3%) patients expressed lower pain thresholds,
of original value \( (\mu = -0.635 \text{ pounds} \pm 0.845 \text{ SD}) \) at the right upper insertion of the masseter muscle (RSM). Meanwhile, after BTX injection, the results were similar. All patients expressed greater pain threshold, 13.29% of the original value \( (\mu = +1.72 \text{ pounds} \pm 0.59 \text{ SD}) \). Contrary to conservative therapy, patients did not show a decrease in pain threshold at any trigger point.

In addition, significant improvements were observed in terms of VAS scores (Fig. 3) evaluated by algometry: for conservative therapy, the improvement was 5.2% \( (\mu = +0.46 \text{ points} \pm 0.35 \text{ SD}) \) in comparison with the average of the whole sample \( (\mu = 8.85 \text{ points} \pm 0.285 \text{ SD}) \); However, there was no difference in pain perception in 5 (45%) patients, 3 (27%) of whom reported an increase in pain perception \(-0.10 \text{ points} \pm 1 \text{ SD}\) in the upper left masseter muscle (LSM). On the other hand, patients who received BTX injections reported an improvement of 19.2% \( (\mu = 1.70 \text{ points} \pm 0.5 \text{ SD}) \) in VAS scores without any side effects during treatment. Nevertheless, there was no long-term follow up.

Pain relief was significantly more pronounced in patients receiving BTX therapy, as evident by both scores (VAS and algometry). No adverse reactions were reported.

**Range opening**

The average interincisal mouth opening at baseline \( (n = 8) \) was 42.3 ± 6.09 mm (range, 31-50 mm). At the 1-month follow up, patients receiving BTX therapy showed improved mouth opening, and the average interincisal mouth opening was 43.4 ± 6.25 mm. The mean difference in mouth opening before and 2 months after both treatments was 1.1 ± 6.5 (2.5% of the original value). No marked changes were observed in interincisal mouth opening at baseline versus conservative therapy \( (42.3 \pm 5.23) \).

**Discussion**

Muscle tenderness on palpation is one of the most important clinical symptoms of masticatory motor system dysfunctions, which occurs in approximately 90% of patients. Manual muscle palpation, considered the “gold standard”, is the most popular and most common clinical method used to evaluate muscle pain (15). However, the primary disadvantages of this method include quantitative assessment of its results and lack of repeatability. A more objective alternative to this method is pressure algometry; it is a diagnostic test that allows quantitative assessment of muscle pain and ensures repeatability of diagnostic factors applied (16,17). Because of the specific nature of examination, pressure algometry is dependent on several factors. A crucial element is maintaining constant test conditions. One of the principal local factors that is particularly important in this respect is the invariable position of the algometer in relation to the examining structures. Other important elements include dynamics of the pressure exerted, area at which the pressure is applied, and differences between algometers (15). Numerous short- and long-term clinical experiments have been conducted by Farella et al. (18) on a group of healthy volunteers and patients with dysfunctions of the masticatory system, wherein less variation was noted in the repeatability of pain threshold during pressure algometry compared with individual variability in this respect. The influence of other factors on pain threshold did not exceed 25% of possible variance. Of note, the prediction interval for pain threshold related to various factors is considerably smaller in comparison with the range of differences.
between healthy subjects and patients with functional disorders of the masticatory system (4-50% of variance). High accuracy and precision of pressure algometry was also confirmed by Bernhardt et al. (19), who conducted a study on 15 healthy volunteers and 15 patients with masticatory motor system dysfunctions and demonstrated high accuracy and repeatability of measurements made using two pressure algometers with an intra-class correlation coefficient ranging 0.73-0.99. Several studies have evaluated the occurrence of increased pain on palpation in structures of the masticatory system in patients with functional disorders. Mohn et al. (20) examined the occurrence of pain under experimental conditions in response to transcutaneous electrical stimulation and pressure algometry; patients with TMDs experienced greater pain in response to electrical stimulation and an increase in pain during an isometric contraction, which was not observed in healthy subjects. According to the authors, increase in pain during isometric contractions may indicate centralization of pain sensitivity in patients with TMJ dysfunction. Another study by Etöz and Ataoğlu (21) showed lower pain thresholds in 50 patients with functional disorders when compared with 45 healthy individuals; significantly lower pain thresholds were observed in patients with <40-mm range of vertical mandibular opening. According to the authors, lower pain threshold can be a manifestation of subjective symptoms of functional disorders in such patients. An algometric study by McBeth and Gratt (22) revealed a significantly greater sensation of pain in the front and middle areas of the temporalis muscle, both regions of the masseter muscles, and lateral surfaces of the TMJ in 20 patients with functional pain disorders compared with 21 individuals without any symptoms of dysfunction. The possibility of using pressure algometry for diagnosing masticatory system dysfunctions was also confirmed by Visscher et al. (23), who conducted a research on 250 respondents, of whom 148 manifested subjective pain symptoms and demonstrated the usefulness of pressure algometry. One abstract (24) (oral presentation) correlates pressure algometry and BTX injections in literature; according to the authors, even when cost of treatment choice is higher, the most effective management could be obtained with botulinum toxin type-A (BTX-A) in myofascial pain syndrome. Despite being more expensive than conservative treatment (e.g., splint), the effectiveness of oral appliances remains debatable, and potential serious side effects have been reported, which include increased muscle activity, increased load on the TMJ, and supraeruption of teeth (25). Furthermore, variability in appliance design and patient cooperation may contribute to inconsistent success rates. To avoid such potential bias, no splint was used in the conservative group, but this will be considered in future research.

Emberg et al. (26) found that BTX produced clinically significant pain-reducing effects (30%) at 1-month follow up by using pressure algometry. Despite these findings, the authors concluded that “BTX is not efficacious as an adjunct in comparison to conservative treatment in patients with persistent myofascial TMD pain.” It should be noted that the aforementioned crossover study (saline vs. BTX) only targeted masseter-standardized points and had a potential disadvantage of patient bias (resulting from expectation of treatment effect), i.e., a patient who experiences pain reduction after the first injection might expect the second injection to be less effective and vice versa; moreover, drug consumption was not withdrawn. Thus, we did not consider a crossover design in our study where patients serve as their own controls; instead, direct comparisons were made between groups (conservative vs. BTX). Another explanation for decreased pain following saline injections may be the needle effect or regression of the condition due to the fluctuating nature of temporomandibular disorders (26). At our hospital, use of dry needle or saline injections to create groups for comparisons was not possible owing to local Ethical Review Board considerations. Moreover, although the results suggest reduction in pain, some pitfalls must be considered, and our study had certain limitations. The sample size was small, which could impact study findings. The study was not blinded either for patients or examiners. The authors will continue this line of research with use of a digital algometer (to improve stability and repeatability of the applied pressure, which enhances the credibility of results obtained), modification of BTX dosage, calculation of sample size, and longer follow up (6 months) to upgrade this pilot study, as suggested in a recent review by Chen YW.

Both conservative therapy and BTX injections are effective and secure options for treatment of myofascial pain. However, according to the results of this study, pain threshold ranges obtained with BTX therapy are better (higher). BTX injections appear to be effective for patients with chronic facial pain targeting masseter and temporalis muscles. For patients who are nonresponsive to conservative therapy, further research will contribute to elucidate benefits from use of BTX therapy.

**Conflict of interest**

None declared.
References