ORIGINAL PAPER

LONG-TERM EFFECTS OF BOTULINUM TOXIN A INJECTION ON PAIN AND QUALITY OF LIFE IN PATIENTS WITH MYOFASCIAL PAIN OF MASTICATORY MUSCLES: A RETROSPECTIVE STUDY

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ABSTRACT

Introduction: Favorable effects of botulinum toxin type A (BoNT/A) on muscle hyperactivity and pain has led to its' use in the treatment of temporomandibular joint disorders, related to muscle pain and masticatory myofascial pain.

Objectives: The aim of this retrospective study was to evaluate the short- and long-term effects of trigger point injections of BoNT/A in patients with myofascial pain syndrome.

Material and methods: The study included 17 individuals aged 19-57 years (mean, 33 years), with 2 years of follow-up records. Visual analogue scale (VAS), pressure-pain threshold (PPT), and maximum mouth opening (MMO) were applied to evaluate pain and dysfunction. Mood and sleep quality were assessed using Beck's depression inventory (BDI) and Pittsburgh sleep quality index (PSQI). All evaluations were repeated before (T0) as well as at 4 weeks (T1), 6 months (T2), and 2 years (T3) after BoNT/A injection.

Results: VAS score was lower at all 3 post-injection time points compared to T0 ($p < 0.001$). Significant increases in PPT and MMO measurements were also observed at T1, T2, and T3 compared to T0. BDI scores were significantly reduced at T1 and T2 compared to T0 ($p < 0.05$). PSQI decreased significantly between T0 and T1 ($p < 0.001$), but increased at T3 ($p < 0.05$).

Conclusions: BoNT/A injections are an effective treatment alternative that relieve myofascial pain and mouth opening restriction, and subsequently improve quality of life in both the short- and long-term.

Key words: myofascial pain, botulinum toxin A, trigger point, depression, sleep quality.

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INTRODUCTION

Temporomandibular joint disorders (TMD) include pain in the temporomandibular joint (TMJ) and adjacent tissues as well as anomalies, such as functional limitations of the mandible and/or jaw clicking. Although the etiological factors involved in TMD have not been clearly identified, it is believed that parafunctional movements, such as bruxism and teeth clenching, and conditions, like stress and anxiety, may cause contraction pain in

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the masticatory muscles as an effect of the inflammation of the joint capsule [1]. TMD may stem from irregularities and disorders of the joint region (intra-articular) as well as irregularities of the surrounding musculature (extra-articular) [2].

Myofascial pain of the masticatory muscles is a condition that affects a large proportion of patients with TMD symptoms [3]. Myofascial pain syndrome is a regional condition of muscle pain and stiffness, characterized by the presence of myofascial trigger points that cause pain due to nociceptor sensitization. Muscle sensitivity on palpation is an important diagnostic sign in masticatory motor system dysfunctions and is present in approximately 90% of patients [4, 5].

TMD and the associated pain are more than a simple feeling of discomfort. Chronic pain and discomfort can affect the mental state of patients, and lead to conditions that impair daily life, such as reduced sleep quality [6-8]. Therefore, long-term planning should be the primary management approach for patients with TMD and masticatory muscle myofascial pain, as it may benefit patients psychologically in addition to relieving their pain.

Treatment of myofascial pain is complex and usually varies based on the symptoms [9]. Primary treatment of myofascial pain in the face may include the use of occlusal splints, supportive patient's exercises, interventions to reduce stress and anxiety, muscle exercises, postural modifications, pharmaceutical therapies (e.g., non-steroidal anti-inflammatory drugs, myorelaxants, benzodiazepines, selective serotonin reuptake inhibitors), alternative therapies, such as acupuncture to reduce symptoms, and botulinum toxin (BoNT) injections [10]. BoNT, which is the exotoxin of a gram-positive bacterium called *Clostridium botulinum*, acts by blocking the release of acetylcholine in neuro-muscular junctions, thereby reducing the activity of muscles and secretory glands [10, 11].

Analgesic effect of botulinum toxin type A (BoNT/A) has been known for many years. This neurotoxin prevents muscle contractions by pre-synaptic blockade of acetylcholine secretion in the motor end plates. This allows decompression of afferent nociceptive neurons and blood vessels [12]. However, analgesic effect of BoNT/A does not occur solely as a result of muscle relaxation. By binding to SNAP25, a member of SNARE protein family, BoNT/A inhibits the formation of SNARE complex, which is required for synaptic vesicle fusion. SNARE proteins are also responsible for the regulation of inflammatory mediators involved in pain modulation, such as calcitonin gene-related peptide (CGRP), substance P, and glutamate [13].

OBJECTIVES

Favorable effects of BoNT/A on muscle hyperactivity and pain led to its' use in the treatment of TMD-related muscle pain and masticatory myofascial pain [3, 4, 10, 11, 13, 14]. Although studies have reported significant reductions in muscle pain with BoNT injection, they were focused on 1- to 6-month outcomes. In light of this information, the objective of this study was to evaluate the short- and long-term effects of BoNT/A trigger point injections in patients with myofascial pain associated with TMD.

MATERIAL AND METHODS

PATIENTS' SELECTION

The study sample comprised patients who presented to the Department of Maxillofacial Surgery of İstanbul Medipol University Oral, Dental, and Maxillofacial Diseases Hospital between September 2014 and May 2017. This study followed the Declaration of Helsinki on medical protocol and ethics and the regional Ethical Review Board of İstanbul Medipol University approved the study (IRB number, 698). A written informed consent was acquired from all patients before the treatment.

During the study period, 140 patients presented with complaints of pain in the perimandibular and temporomandibular regions while at rest and/ or during movement, restricted mouth opening and difficulty in chewing, and pain and tenderness upon palpation of the masticatory muscles. Data were collected from these patients' treatment records and archive materials. According to these sources, clinical improvement was achieved in 90 patients with conservative primary treatments, including occlusal splints, soft diet, massage, habitual modifications, and pharmaceutical therapy. BoNT/A injection was recommended to 50 patients whose pain and other symptoms persisted, of whom 35 patients consented. Ten of these patients underwent arthrocentesis in addition to BoNT/A therapy, and were not included in the study. Three patients with orofacial dystonia and five patients with incomplete records were also not included in the study group. As a result, the study sample consisted of 17 individuals (14 females, 3 males) aged 19-57 (mean, 33) years, who had regular/complete records from at least 2 years of follow-up.

Myofascial pain syndrome diagnosis was made according to Travell and Simons' criteria, according to which five major and at least one minor criteria are required for clinical diagnosis [15]. Patients whose symptoms persisted for at least 6 months and did not respond to conservative treatment were included in this study.

Patients who had previously undergone open jaw surgery, underwent arthrocentesis, or were injected with intra/ periarticular drugs were excluded from the study.

ASSESSMENTS

In this study, visual analogue scale (VAS), pressure-pain threshold (PPT), and maximum mouth opening (MMO) were applied to evaluate pain and dysfunction, while Beck's depression inventory (BDI) and Pittsburgh sleep quality index (PSQI) were used to assess TMD-related emotional state and sleep quality, respectively. All evaluations were performed at four different time points, such as before BoNT/A injection (T0) and at 4 weeks (T1), 6 months (T2), and 2 years (T3) after BoNT/A injection.

VISUAL ANALOGUE SCALE

Patients were asked to indicate their pain level on a 10-cm scale marked 'no pain' on one end and 'unbearable pain' on the other, and the points marked by the patients were evaluated.

PRESSURE-PAIN THRESHOLD

An algometer is a device that applies force to the tissue through small plastic tips in order to measure soft tissue sensitivity. PPT is the minimum force that causes pain [16]. In this study, incremental pressure was applied to patients, and the lowest force described as painful was recorded as their PPT.

MAXIMUM MOUTH OPENING

With patient's mouth opened as wide as possible without the application of external force, the distance between the peaks of the upper and lower incisors was measured with a ruler and recorded.

BECK'S DEPRESSION INVENTORY

BDI is a 21-item, multiple-choice, self-reported inventory used to assess depression severity. Each question has 4 answers worth 0-3 points, and the responses are summed to obtain a total score. Higher total scores are assumed to indicate more severe depression [17]. BDI scores of patients included in the study were calculated to determine whether TMD and myofascial pain were related to depression.

PITTSBURGH SLEEP QUALITY INDEX

PSQI is a self-rated questionnaire used to evaluate sleep quality. It consists of 7 sub-sections that are scored between 0 and 3 for a global score ranging from 0 to 21. Scores of 5 or higher indicate low sleep quality [18, 19]. Patients in the study completed PSQI, and their global scores were recorded to assess sleep quality.

BOTULINUM TOXIN TYPE A INJECTION

After locating trigger points using palpation and algometer, BoNT/A (Allergan BOTOX®, Westport, Ireland) was diluted in 2 ml of saline and injected into the masseter and temporal muscles at a dose of 10-15 IU at each trigger point. A maximum of 100 IU was injected bilaterally into the masseter and temporal muscles. Injection into the lateral pterygoid muscle was not performed due to difficulty in localizing of the lateral pterygoid muscle.

STATISTICAL ANALYSIS

Data obtained from this study were evaluated using SPSS version 17.0 software package (SPSS Inc., Chicago, Illinois, USA). A paired samples *t*-test was used to analyze differences in the assessed parameters between the evaluated time points. *P*-value < 0.05 was accepted as the level of significance.

RESULTS

The mean VAS score was significantly lower at T1 (4 weeks post-injection), T2 (6 months post-injection), and T3 (2 years post-injection) compared to T0 (pre-injection) ($p < 0.001$). However, VAS score increased significantly between T1 and T3 ($p < 0.05$). Similarly, there were significant differences in PPT and MMO measurements at T1, T2, and T3 when compared with T0 values (Table 1).

BDI scores decreased significantly at T1 and T2 compared to T0 ($p < 0.05$), but increased significantly between T2 and T3 ($p < 0.05$). PSQI score showed a highly significant decrease between T0 and T1 ($p < 0.001$), but increased significantly between T1 and T3 ($p < 0.05$) (Table 1).

DISCUSSION

Myofascial pain syndrome is a regional disorder characterized by progressive muscle pain and stiffness and the presence of myofascial trigger points [20]. Myofascial pain in the facial region is often associated with TMD, and masticatory muscle spasms may also cause functional limitations [10, 12].

Numerous studies investigating the efficacy of BoNT/A in relieving TMD-related muscular pain and masticatory muscle myofascial pain have been published in recent years [3, 4, 10, 11, 14, 16]. While BoNT/A has both pre-synaptic and post-synaptic activity at the neuromuscular junctions, it mainly acts by inhibiting acetylcholine release, without affecting impulse conduction at the nerve terminals [21]. Although BoNT/A has shown remarkable efficacy on myofascial pain of the masticatory muscles,

TABLE 1. Descriptive statistics and comparison of mean values of parameters between observation periods

	Descriptive statistics				Paired *t*-test									
	T0 ($n = 17$) X ± SD	T1 ($n = 17$) X ± SD	T2 ($n = 17$) X ± SD	T3 ($n = 17$) X ± SD	T1-T0		T2-T0		T3-T0		T2-T1		T3-T1		T3-T2	
					p-value	Test	*p*-value	Test	*p*-value	Test	*p*-value	Test	*p*-value	Test	*p*-value	Test
Visual analog scale (VAS)	7.88 ± 2.02	2.29 ± 1.44	2.88 ± 2.66	3.58 ± 2.89	0.000	***	0.000	***	0.003	***	0.214		0.024	*	0.138	
Pressure pain threshold (PPT; kg/cm^2)	3.75 ± 1.39	5.88 ± 1.36	5.52 ± 1.32	5.25 ± 1.72	0.000	***	0.000	***	0.000	***	0.138		0.072		0.135	
Maximum mouth opening (MMO; mm)	36.64 ± 6.43	41.05 ± 6.77	40.94 ± 8.16	40.23 ± 7.83	0.000	***	0.020	*	0.042	*	0.906		0.445		0.157	
Beck depression inventory (BDI)	14.47 ± 7.53	12.00 ± 8.29	11.94 ± 7.75	13.17 ± 7.82	0.022	*	0.021	*	0.146		0.894		0.058		0.022	*
Pittsburgh sleep quality index (PSQI)	4.88 ± 2.42	3.47 ± 1.87	4.05 ± 2.48	4.29 ± 2.41	0.001	***	0.110		0.221		0.154		0.03	*	0.299	

*Paired t-test; *p < 0.05; **p < 0.01; ***p < 0.001; X – mean value; S_x – error of mean*

study end-points have usually been based on outcomes at 6 months or less. To the best of the authors' knowledge, this was the first study to investigate both the short- and long-term effects of BoNT/A on the masticatory muscles.

Pain assessment is the first and most important step of pain management. In the VAS method, one of the one-dimensional scales used to assess pain, patients rates their own pain between 'none' and 'unbearable' by placing a mark on a ruled line. It is a sensitive and easy to understand method [22]. Therefore, VAS was applied to assess pain in the present study. Results of the present study showed that myofascial pain decreased significantly at 4 weeks (T1), 6 months (T2), and 2 years (T3) after BoNT/A injection compared to initial levels. Although pain increased significantly between T1 and T3, it never returned to pre-injection level. In a placebo-controlled trial including 90 patients, Von Lindern *et al.* [11] reported a 3.2-point decrease in VAS score over a 4-week observation period. Pihut *et al.* [14] observed a marked reduction in the masseter muscle pain at 6 months after BoNT/A injection. In the present study, we observed significant increase in PPT at all post-injection time points compared to pre-injection values. In a study evaluating the effects of Botox injection on 384 patients with myofascial pain syndrome, Günther and Bitterlich [23] observed a decrease of more than 2 points in VAS scores in about half of patients at 1 week after injection, and reported a decrease in pain intensity in 95% of patients at 6 weeks. They also noted that PPT increased by an average of 0.6. Short-term results of the present study are consistent with findings of these studies, and confirm the benefit of trigger point BoNT/A injections in myofascial pain of the masticatory muscles.

Meral *et al.* [10] stated that in addition to marked improvement in masticatory myofascial pain, BoNT/A injection also resulted in an improvement in MMO. They attributed the increase in MMO to muscular relaxation and reduced muscle inflammation that occur due to BoNT injection. Consistent with their results, it was also observed a marked improvement in mouth opening at all time points compared to pre-injection values. An important point to consider is that changes in MMO were consistent with changes in VAS scores and PPT values. Therefore, it can be assumed that BoNT/A injection causes an increase in mouth opening in association with a reduction in muscle hyperactivity and pain.

Mandibular bone loss and changes in bone structure are thought to be important potential side effects of BoNT/A injections to the masticatory muscles. According to functional matrix theory, changes in the size, shape, and position of skeletal units and even the formation of these units, occur as a result of changes in the relevant functional matrices. In other words, the skeleton is shaped by its' function [24]. Therefore, just as muscular hyperactivity may lead to osseous changes, decreased muscle function may also result in changes in bone structure. Animal studies have shown that in addition

to changes in muscle fibers, BoNT injection to the masticatory muscles can result in major ramal, condylar, and alveolar bone loss, which in turn may increase the risk of bone fractures [25, 26]. Kahn *et al.* [27] stated that bone loss and/or bone formation may be observed at 1 year after BoNT injection due to changes in intensity and location of muscle tension. Pihut *et al.* [14] believe that 6 months after injection, the effects of the neurotoxin may decrease, resulting in recurrent pain and the need for repeated doses. They argued that in order to avoid possible effects on the bones, BoNT/A injections should be considered as a secondary treatment and applied at minimal doses. However, the results of the present study indicate that favorable changes in pain score, PPT, and MMO values compared to pre-injection levels persist even 2 years after injection. Although the effect is somewhat diminished compared to the results seen immediately after administration, it suggests that BoNT/A injections can be effective even in the long-term. Therefore, the side effects and need for repeated doses discussed in previous studies may be less than expected.

Although the etiology and pathogenesis of TMD are multifactorial, it has long been suspected that chronic facial pain may be associated with depression and stress, and various ideas on this topic have been proposed [6, 7]. According to Banks and Kerr [28], depression may occur secondarily to chronic pain. On the other hand, Kindler *et al.* [29] stated that depression and anxiety symptoms should be regarded as risk factors for TMD-related pain. In addition to the psychological effects of chronic pain, other effects that impact patient comfort are also reported, such as impaired sleep quality [30].

Based on these views, one of the aims of the present study was to assess emotional state and sleep quality, and determine whether these variables are related to myofascial pain. In the patient group of the present study, psychological well-being as measured by BDI improved at both 4 weeks and 6 months post-injection compared to pre-injection level, while there was a slight increase between 6 months and 2 years. Sleep quality assessed using PSQI improved markedly at 4 weeks compared to the pre-injection period, but similarly was slightly higher at 2 years compared to 4 weeks. BDI and PSQI assessments were also consistent with pain scores. This suggests that pain is associated with depression and sleep quality. However, more comprehensive studies considering other parameters that may affect mental state and stress are needed to reach a more definite conclusion.

LIMITATIONS

One of the most important limitations of the present study was the absence of a control group. However, for ethical reasons, keeping patients with active pain under observation for 2 years without treatment is not a correct approach.

CONCLUSIONS

BoNT/A injections are shown to be effective in relieving TMD-related myofascial pain and pain-related mouth opening restriction, thus improving patients' psychological well-being. Although these effects are more pronounced in the short-term, it is noteworthy that even after a 2-year of follow-up period, the results were significantly better compared to pre-injection levels. BoNT/A injections yield favorable outcomes even in the long-term, and should cause fewer side effects due to reduced frequency of repeated doses. Therefore, BoNT/A can be considered an effective method for the treatment of myofascial pain of the masticatory muscles. However, further prospective studies with larger numbers of patients may be useful to obtain more detailed information.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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