AJDS LAZHAR Al-Azhar Journal of Dental Science
Vol. 25- No. 3- 301:310- July 2022
Print ISSN 1110-6751 | online ISSN 2682 - 3314
https://ajdsm.journals.ekb.eg
Oral Biology, Medicine & Surgical Sciences Issue *(Oral Biology, Oral Pathology, Oral Periodontology, Medicine, Oral & Maxillofacial Surgery)*

EVALUATION OF BOTULINUM TOXIN INJECTION IN MASTICATORY MUSCLES FOR MANAGING TEMPOROMANDIBULAR DISORDERS PAIN

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ABSTRACT

Objective: To evaluate injection of botulinum toxin in masseter and temporalis muscles as a treatment modality for temporomandibular disorders pain. **Subjects and Methods:** A total of 14 patients diagnosed with TMD were selected from the Out-Patient Clinic of the Oral Surgery Department at Faculty of Dental Medicine, Cairo-boys, Al-Azhar University, Egypt. Study included patients with myofascial pain, pain associated with disc displacement with reduction, pain associated with hypermobility of the T.M.J. Patients with unilateral or bilateral disease were accepted equally. They were divided into 2 groups study group which received the botulinum toxin injections and control group which received 0.9% saline solution. Patients had 4 follow ups in total first at the injection session then after 1 month, after 3 months and after 6 months post injection. 4 parameters were recorded Pains scores on the VAS, vertical mouth opening, Tenderness to palpation and Masseter muscle activity using EMG. **Results:** Results revealed that, there was statistically a significantly lower pain values and increased mouth opening reported after 6 months of botulinum toxin injection. **Conclusion:** the injection of botulinum toxin is effective in decreasing pain and increasing mouth opening in patient diagnosed with TMDs.

KEYWORDS: botulinum toxin, temporomandibular disorders, pain relief.

INTRODUCTION

Temporomandibular disorders (TMDs) is a collective term used to describe a group of conditions involving the temporomandibular joint (TMJ), masticatory muscles and associated structures. Causative factors identified for TMD include aberrant masticatory muscle activity, trauma, psychological factors, and diseases such as arthritis [(1)].

TMD problems are characterized by pain in the preauricular region that is commonly aggravated by jaw function. The pain is often accompanied, either singly or in combination, by limitation of jaw movement, joint sounds, palpable muscle tenderness, or joint soreness. TMDs are limited to pain and dysfunction arising in and from the masticatory musculoskeletal system [(2)].

Mejersjo and Carlson [(3)] pointed out that clinical experience and longitudinal studies indicate that a small proportion of patients with TMJ dysfunction do not improve with conventional stomatognathic

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DOI: *10.21608/ajdsm.2021.59343.1153*

methods. Kopp [4] stated that "the most plausible explanation seems to be that factors other than occlusion. Such as general muscle tension and general joint/muscle reaction, in combination with psychological factors, play a major role in these patients".

Because many cases of TMD include a clinical history of muscular activity such as clenching or bruxism, an inhibition of this activity through a partial paralysis of the appropriate muscles could possibly yield significant therapeutic gains [5]. The importance of the role of muscles and ligaments is receiving much greater recognition than in earlier years, as a result, treatment has moved away from the surgical to a more conservative approach [6]. Temporomandibular disorders (TMDs) affect the face and jaws, and cause chronic pain and dysfunction in many people. As in other conditions involving the musculoskeletal system controlling the myogenous component is an integral part of treatment [7]. Botulinum toxin A (BTX-A) is a new neuromuscular blocker that has recently been used successfully for the treatment of TMDs [7].

Strains of Clostridium botulinum produce 7 structurally similar but antigenically distinct serotypes of neurotoxin designated A through G. The toxins exert their effects by inhibiting the release of the neurotransmitter acetylcholine at peripheral neuromuscular functions and synapses, causing flaccid paralysis. Onset of action is within 24 to 48 hours and duration of action has been reported to be 1 to 6 months. [9]

Botulinum toxin was first used in the 1970s to weaken extraocular muscles in the treatment of strabismus by direct injection of the muscles to be paralyzed [10]. In the mid-1980s other conditions such as blepharospasm [11], hemifacial spasm [12], oromandibular dystonia (an ailment found in conjunction with Meige syndrome, which can present with abnormal eyelid and facial movements [13], segmental and generalized tremors were treated with botulinum injections [14].

Correction of facial asymmetry due to facial nerve paralysis also was reported using this modality [15].

In 1990 botulinum toxin type A has been approved by the Food and Drug Administration [FDA] as a safe and effective therapy for blepharospasm, Strabismus, spasmodic dysphonia, oromandibular dystonia, cervical dystonia and neuromuscular disorders of the facial nerve [16].

Nowadays, after the FDA approved botulinum toxin injections have been widely used successfully for the above- mentioned diseases [17].

Recently, BTX-A has proven to be a dramatically successful new form of cosmetic therapy as it has been shown to be a reliable and reversible means of treating wrinkles and lines from hyperkinetic muscles of facial expression [18]. Treatment of masseteric hypertrophy has also been reported for cosmetic purposes [19].

Botulinum toxin therapy has been reported to alleviate pain associated with various conditions with or without concomitant excessive muscle contractions. Tension-associated headaches have been reported to be alleviated with BTX-A therapy and may be effective for cervicogenic headache and chronic low back pain associated with muscle spasm [20].

The aim of this study was to test the hypothesis that BTX injection of botulinum toxin in masseter and temporalis muscles is more effective than isotonic saline for the relief of persistent TMD pain.

SUBJECTS AND METHODS

Sample Size

A sample size of 14 has 80% power to detect a difference between means of 0.70 with a significance level (alpha) of 0.05 (two-tailed).

Patient selection

A total of 14 patients diagnosed with TMD were selected from the Out-Patient Clinic of the Oral

Surgery Department at Faculty of Dental Medicine, Cairo-boys, Al-Azhar University, Egypt. Study included patients with myofascial pain, pain associated with disc displacement with reduction, pain associated with hypermobility of the T.M.J. Patients with unilateral or bilateral disease were accepted equally. After through preoperative examination and patient's medical history was thoroughly checked and reviewed and the eligibility for the study was confirmed. Patients were randomly distributed into 2 groups

1. Study group: Botulinum toxin

Botox reconstitution:

100-unit vial botulinum toxin (Allergan, USA) stored at a temperature of -4c and was reconstituted right before injection was made. The vial was reconstituted with 2ml saline to obtain 5 unit/0.1ml reconstituting the Botox vial the saline was not pushed into the vial with pressure but rather allowed to be drawn in the vial by the vacuum so as to avoid bubbling or frothing that can inactivate the toxin. the saline was not shaken to mix the toxin instead the vial was gently rolled back and forth between the palm

The intramuscular injections were performed with the patient awake in the clinic. The skin was wiped with an alcohol swab. the masseter muscle palpated at its insertion at the angle and body of the mandible. Two injections were given 1 cm superior to the inferior border of the mandible and two other injections were given 1 cm inferior to the inferior border of the zygomatic arch. A fifth injection was given in the center of the masseter muscle (Fig. 1:A). One more injection was given 1 cm inferior to the origin of the temporalis muscle (Fig. 1:B). Using a 1cc TB syringe and a 30-gauge needle. The subject thus received 100 units of reconstituted botulinum toxin A 35 units were injected into each masseter muscle and 15 units into each temporalis muscle.

2. Control group: 0.9% Sodium Chloride Injection

The same procedures were carried out as the study group. The only exception is that the subjects received unpreserved 0.9% sodium chloride (Almottahedon, Egypt) instead of botulinum toxin as a placebo.

All patients had received bilateral injections. Injections were made within the muscles and to avoid superficial injections the needle was inserted down to bone level and then withdrawn by about 2mm (temporalis muscle) to 5mm (masseter muscle) to ensure that the needle was in the bulk of the muscle. To distribute the toxin as evenly as possible in the masseter muscle, injections were made both in the region of the zygomatic arch and on the mandibular angle. All injections were made after negative aspiration of the syringe on all sites of injection, especially the temporalis muscle to avoid the superficial temporal artery and its branches.

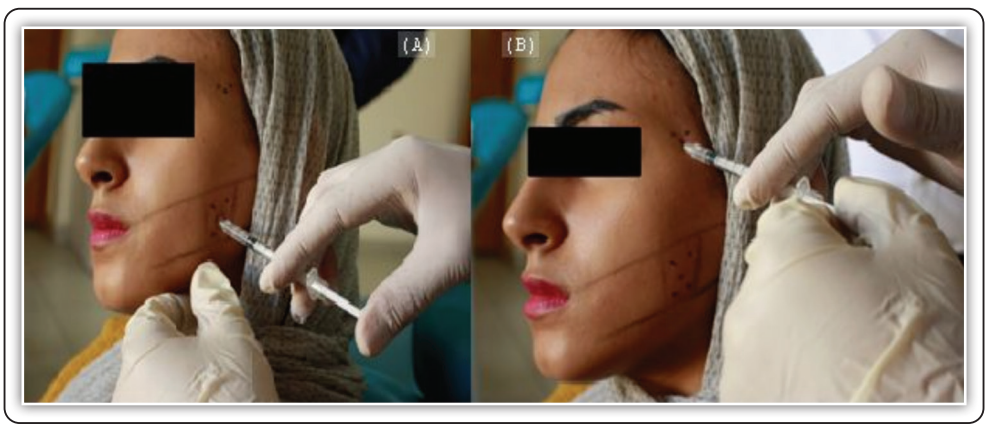

FIG (1) (A): Injection of BTX-A in the masseter muscle, (B): injection of the temporalis muscle

Some injections caused spot bleeding which was controlled easily with pressure. The important point was to stop leaking of the injected toxin. In effort to prevent unwanted migration of the toxin to adjacent areas, patients were instructed to avoid rubbing the injection site and to stay vertical for at least 4 hours after injection to prevent unwanted diffusion of toxin to unwanted areas. Patients were instructed to avoid aspirin, aspirin-containing products and products that inhibit platelet function for 7 to 10 days before injection to minimize postoperative ecchymosis.

Postoperative evaluation:

Follow up visits were carried out at 1,3,6 months postoperatively. Bringing the total number of follow ups to 4 (including the initial assessment), Assessment at each visit included:

1. Subjective pain scores: Where based on visual analog scale (VAS), where 0 is no pain and 10 is the worst facial/jaw pain.
2. Range of motion measurement: Maximum vertical mouth opening measured with a Boley's gauge between the same upper and lower anterior tooth at each visit
3. Tenderness to palpation: It was recorded in the temporalis, masseter and the TMJ capsule bilaterally

   Examining the muscles and joint capsules for tenderness requires the application of pressure using the spade-like pad of the distal phalanx of the right index finger while using the left hand to brace the head for stability. With the patient's mandible in resting position, the muscles were palpated in a passive state. As needed, patients were asked to clench and relax to identify and to insure palpation of the correct muscle site. Because the site of maximum tenderness may vary from patient to patient. It was important to press in multiple areas in the muscle specified to determine if tenderness exists. Reaction to pressure was graded from 0 to 3 in which (0) represented no discomfort on firm palpation and (3) sever discomfort with minimal pressure.
4. Masseter muscle activity: Muscle activity was measured using NEXUS 10 by mindmedia (Fig. 2: A) before injection and at 1,3,6 months after injection. To ensure accurate recording of muscle activity at assessment time the same point of recording was used at each visit (Fig. 2: B)

Statistical analysis:

Statistical analysis was then performed using a commercially available software program (SPSS 18; SPSS, Chicago, IL, USA).

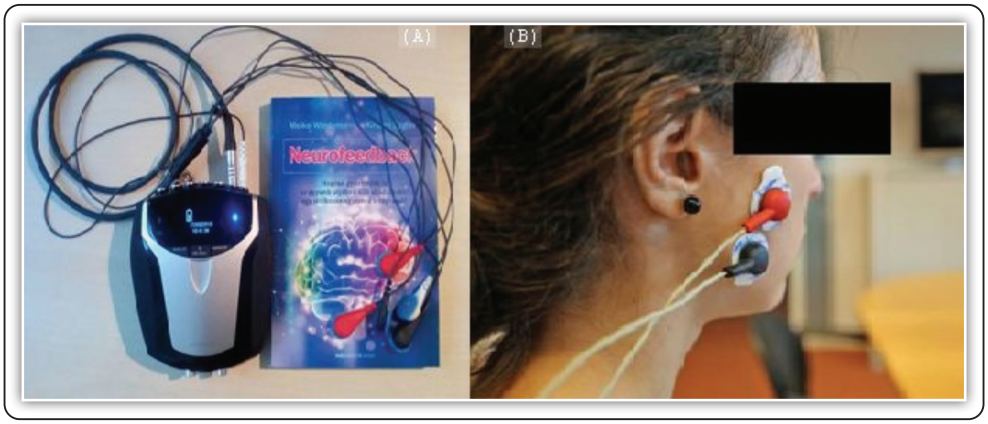

FIG (2) The device used to record masseteric EMG, (B): placement of pads to record masseteric EMG

Values were showed as mean and standard deviation (SD). Data were explored for normality using Kolmogorov-Smirnov test of normality. For parametric data, independent test was used for comparison between groups (inter-group). Repeated measures ANOVA was used for intra-group comparison (within the same group). Paired t test was used for pairwise comparison of different observations.

Most values of difference percent change were non-parametric and were compared between groups using Mann Whitney U test.

The level of significance was set at $P \leq 0.05$.

RESULTS

Comparison between groups

Pain score: At the first visit, there was no significant difference between both groups (p=0.69). In the 2nd, 3rd and 4th visit, a higher mean value was recorded in control group (p=0.00), (Table 1, Fig. 3)

Tenderness to palpation: At the first visit, there was no significant difference between both groups (p=1). In the 2nd, 3rd and 4th visit, a higher mean value was recorded in control group (p=0.00, p=0.002, p=0.001 respectively) (Fig. 4).

TABLE (1) Comparison of mean value of both groups at each observation time (Independent t test)

		First visit		Second visit		Third visit		Forth visit	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Pain score	Control	6.29	1.50	7.00	1.15	6.29	1.25	6.43	1.40
	Botox	6.57	1.13	2.86	1.46	1.14	1.07	1.00	1.00
	P value	5ns 0.69		0.00*		0.00*		0.00*	
Tenderness to palpation	Control	2.14	.69	2.00	.58	2.00	.82	1.71	.76
	Botox	2.14	.69	.57	.53	.43	.53	.00	.00
	P value	1 ns		0.00*		0.002*		0.001*	
Range of motion	Control	27.86	3.44	27.71	2.87	27.29	3.64	28.00	2.89
	Botox	26.71	2.98	31.00	2.52	32.71	2.14	33.71	1.80
	P value	0.519 ns		0.042*		0.007*		0.001*	
EMG	Control	688.86	326.32	650.57	277.72	685.43	215.91	695.29	203.30
	Botox	678.86	365.50	325.71	139.27	264.57	165.61	451.57	142.35
	P value	3ns 0.97		0.017*		0.0014*		0.023*	

*Significance level p≤0.05, * significant, ns=non-significant*

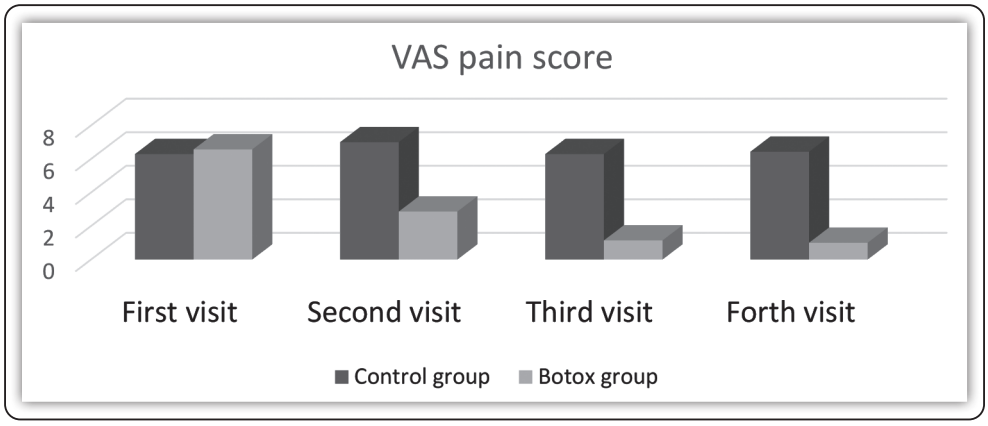

FIG (3) Bar chart of VAS pain score

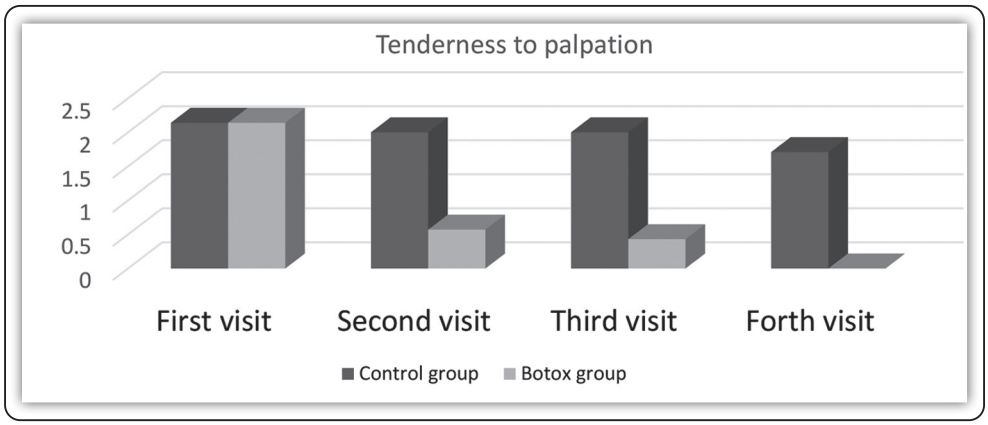

FIG (4) Bar Chart of Tenderness to palpation

Range of motion: At the first visit, there was no significant difference between both groups (p=0.519). In the 2nd, 3rd and 4th visit, a higher mean value was recorded in Botox group (p=0.042, p=0.007, p=0.001 respectively) (Fig. 5).

EMG: At the first visit, there was no significant difference between both groups (p=0.973). In the 2nd, 3rd and 4th visit, a higher mean value was recorded in control group (p=0.017, p=0.0014, p=0.023 respectively (Fig. 6).

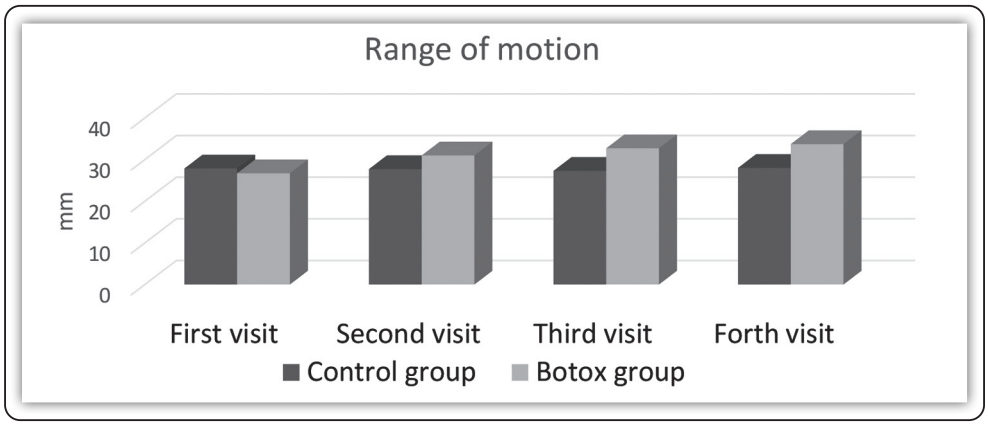

FIG (5) Bar chart for Range of motion

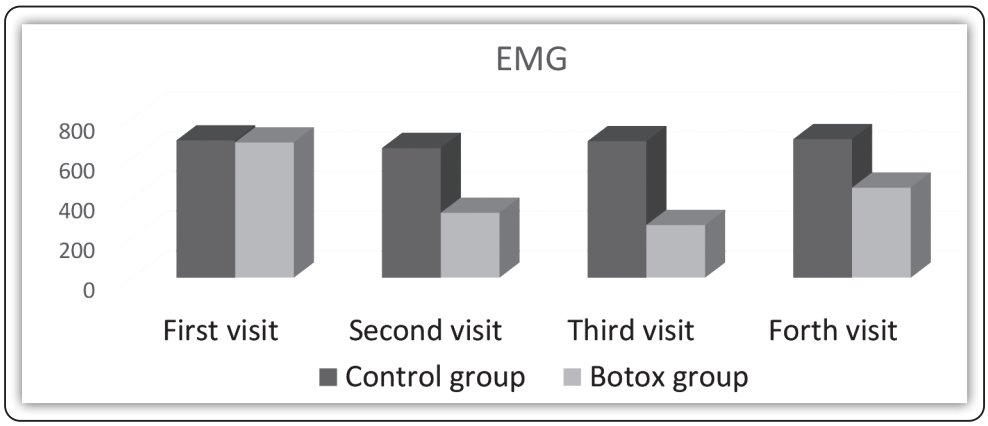

FIG (6) Bar chart for EMG

DISCUSSION

TMD problems are characterized by pain in the preauricular region that is commonly aggravated by jaw functions. The pain is often accompanied either singly or in combination by limitation of jaw movements, joint sounds, palpable muscle tenderness or joint soreness. TMDs are limited to pain and dysfunction arising in and from the masticatory musculoskeletal system [21].

Although TMD begins as functional muscular disorder, it ultimately can cause degenerative changes and internal derangement in the TMJ [22].

Botulinum toxin A, one of eight subtypes of a potent biological toxin produced by clostridium botulinum, is a presynaptic neurotoxin, which causes dose-dependent weakness or paralysis in skeletal muscle by blocking the Ca2+ mediated release of acetylcholine from motor nerve endings. This functionally denervates the affected portions of the muscle [23].

The primary effect is on α motor neuron function, but may also affect the γ motor neurons in the muscle spindles, resulting in lower muscle resting tone. Reversal of local paralysis occurs initially by neural sprouting with reinnervation of the muscle and ultimately by regeneration of the Ach vesicle docking proteins. Which restores function in 1 to 6 months [24].

Botulinum toxin A has been successfully used for diseases with increased muscle tone for about 30 years. BTX-A has been used extensively in the treatment of blepharospasm[25], strabismus, hemifacial spasm[26], spasmodic torticollis[27], oromandibular dystonia [28], spasmodic dysphonia[29], myofascial pain[30] temporomandibular dislocation[31] and temporomandibular disorders [32].

Systemic side effects and local complications are uncommon with BTX-A and rarely reported. They are generally not dose related and can include transient weakness, nausea and pruritis. There were no reported cases of systemic toxicity in our study.

Failure to achieve effective muscular relaxation may be due to several causes. Low concentration of active toxin in the vicinity of the motor end plate is a major concern. It has been shown that deposition of BTX-A 0.5 CMS from a motor end plate results in 50% decrease in muscle fiber paralysis compared with paralysis achieved with direct deposition. Other significant causes of failure include the presence of antibodies to BTX-A as well as improper reconstitution and storage of the drug [33].

Control group Pain score showed no differences in subjective pain scores over the follow up period and any changes in pain were not statistically significant (p=0.841). Tenderness to palpation showed slight decrease in tenderness for some patients but that also was not statistically significant (p=0.437) and was not related to injection as not all patients had similar effect as some also had increased tenderness over the follow up period. Range of motion showed no change in the interincisal measurement for the control group that could have been indicator of any improvement or worsening and have any statistically significance (p=0.609). Measurement of mean maximum voluntary contraction which were recorded by the EMG showed no statistically significant change

In the study group the injection of BTX-A into the masseter and temporalis muscles of patients diagnosed with TMD yielded several significant findings. Pain scores showed a reduction in subjective pain (VAS) in many patients. In all cases of pain reduction, the improvement was noted to happen at the same time as objective and subjective weakness of the masticatory muscles and not before. That is, pain relief closely follows the muscular effect of BTX-A at onset but, importantly, persists beyond the loss of muscle weakness.

The possible mechanisms for these observations are speculative, but two known BTX-A specific events occur; inhibition of α motor neurons resulting in a reduction in the maximum contractile force of the injected muscles, and inhibition of

γ afferents resulting in a reduction in the resting muscle tone. One or both of these mechanisms may be responsible for reducing the mechanical stimulation of sensitized peripheral nociceptive afferent pathways [34].

There is evidence that patients with TMD may have more schedule-induced oral habits, so by reducing both the power and duration of effective contraction of the injected muscles, BTX-A may indirectly inhibit centrally motivated painful muscular activity.

The reduction in muscle activity could also be indirectly responsible for peripherally altering the release of neuropeptides and modulators of local inflammation in such a way that they reduce the stimulation of central wide dynamic range neurons and nociceptive specific neurons. This could happen in the muscle as well as in the TMJ through reduced joint loading [35].

Tenderness to palpation scores also showed the most consistent improvement with time. The mechanism in which pain reduction happens in the injected muscles is not obvious, but the results clearly show that muscles treated with BTX-A are less tender to palpation.

Range of motion: All patients experienced some degree of improvement in maximum range of vertical motion. This observation can be based on three possible mechanisms.

1. Given the reduced tone of the flexor muscles secondary to inhibition of both γ and α neurons, it would be expected that these muscles could be stretched further [36].
2. Inflammation of the muscles would increase viscoelastic tone and therefore the stiffness of a muscle. Inflammation of the TMJ, especially the capsule and supporting ligaments, also reduces the range of movement as in other injured joints[37].
3. Most patients noted that their limitation in jaw opening is secondary to pain centered around the jaw joints. It is likely that reduction in pain also help increase range of motion.

Our results are also in accordance with those of Freund [7] who treated 46 TMD patients with BTX-A 150 U where both masters muscles were injected with 50 U each and temporalis muscles with 25 U each. Subjects were assessed at 2 weeks interval for a period of 8 weeks.

Also results of the present study are also in accordance with those of Von Lindern [38] who treated 90 patients (60 verum and 30 placebo) with chronic myofascial pain (caused by hyperactivity of the masticatory muscles and parafunctional movements) with botulinum toxin A injection in a prospective, single-blinded, randomized placebo-controlled study.

Outcome measures included subjective assessment of pain by visual analog scale (VAS), measurement of mean maximum voluntary contraction (MTC), interincisal opening and tenderness to palpation based on multiple VASs. Medians of the data were taken for each outcome measure at each time point and subjected to Duncan's multiple range tests.

The results showed significant ($P<0.05$) differences in all median outcome measures between the treatment assessment and the three follow-up assessments for the botox group

These results strongly suggest that BTX-A reduced the severity of symptoms and improved the functional abilities for patients with TMD and that these extend beyond its muscle relaxing effects [10].

The results of the present-day study go hand in hand with those of **Freund and Schwartz** [32] who treated 60 patients with chronic TMD (where 46 subjects had co-existing chronic tension-type headache). Subjects were followed on 1,3 and 6 months after injection. Outcome data collected included pain specific to the face and jaws and headache pain by VAS. Data were also collected

on the number of pain free days per month for both facial pain and headache [32].

The results showed that 38 of the 60 patients (63%) reported a 50% improvement in their facial pain during the follow up period. The subset of 46 patients with chronic tension headache and TMD symptoms reported a 50% or greater improvement in headache pain as well. The number of days without headaches also improved post injection [32].

The findings in this study also pose a number of questions about the role that muscles have in the generation of facial pain. If it is accepted that the only pharmacological activity of BTX-A is at the motor end plate, then muscle activity must be seen as a serious determinant of facial pain. The mode of transmission of pain is not clear but may act by the chemical sensitizing of nerve endings in the fascia within the muscle, which then become responsive to minimal chemical or mechanical stimuli.

CONCLUSION

Based on the results of the current study, the following conclusion could be made:

1. Botulinum toxin A was safe and efficacious for the management of patients with muscular TMDs and its effect extend beyond its muscle-relaxing effects.
2. This study revealed also that botulinum toxin therapy can alleviate pain of arthrogenic origin and that was indirectly achieved through the prolonged joints sparing effect of diminished loading secondary to the decreased ability of the musculature to affect joint loading.
3. The results strongly suggest that BTX-A reduces the severity of symptoms and improves the functional abilities for patients with TMD.
4. This study has also revealed that pain experience rather than muscular spasm is more responsible for functional disability in TMD patients.
5. The present study also indicates that the RDC/TMD contain well-defined definition for diagnosing the most common forms of TMDS.

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