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Research

Management of Botulinum Toxin in Masticatory Muscles for Managing Temporomandibular Disorders Pain

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ABSTRACT

Objectives

To evaluate injection of Botulinum toxin in masseter and temporalis muscles as a treatment modality for temporomandibular disorders pain.

Patient and Method

This study consisted of 14 patients divided into two groups. Study group which includes injecting the masseter muscle with Botulinum toxin. While, control group which includes injecting the masseter muscle with 0.9% sodium chloride.

Results

All 14 patients completed the study with no reported worsening of their conditions after treatment. Study group showed that there were significant differences between the pre-treatment values and post-treatment values in all measured values. Control group showed no significant change between pre-treatment and post-treatment.

Conclusion

Botulinum toxin A was safe and efficacious for the management of patients with muscular TMDs and its effect extends beyond its muscle-relaxing effects, can alleviate pain of arthrogenic origin and reduces the severity of symptoms and improves the functional abilities for patients with TMD.

Keywords: *Temporomandibular Disorders Pain, Botulinum Toxin Injection and Masticatory Muscles.*

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]

Temporomandibular disorders (TMDs) affect the face and jaws.[2] In 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.[3]

TMD problems are characterized by chronic pain and dysfunction arising 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 play a major role in these patients". 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.[4,5]

Botulinum toxin A (BTX-A) is a new neuromuscular blocker that has recently been used successfully for the treatment of TMDs. Botulinum toxin A is the exotoxin of a gram-positive bacteria called clostridium botulinum that blocks the release of acetylcholine into the neural junction and leads to reduced activity of the muscles and glands. Onset of action is within 24 to 48 hours and duration of action has been

reported to be 1 to 6 months.[6]

Botulinum toxin type A has been approved by the Food and Drug Administration [FDA] as a safe and effective therapy for blepharospasm,[7] hemifacial spasm,[7] oromandibular dystonia (an ailment found in conjunction with Meige syndrome, which can present with abnormal eyelid and facial movements,[8] segmental and generalized tremors. Strabismus, spasmodic dysphonia, oromandibular dystonia, cervical dystonia and neuromuscular disorders of the facial nerve.[9-11]

Nowadays, after the FDA approved botulinum toxin injections have been widely used successfully for the above- mentioned diseases.[12]

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.[13] Treatment of masseteric hypertrophy has also been reported for cosmetic purposes.[14] 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.[15]

Recent studies on the use of botulinum toxin-AS in TMD has shown that BTX-A is effective in the treatment of some patients with TMD and no significant side effects occurred.[16]

PATIENT AND METHOD

This study included 14 patients diagnosed with TMD between the ages of 23 and 54 years. They were selected from those attending the outpatient clinic of Oral and Maxillofacial Surgery Department, Faculty of Dental Medicine Boys, Al-Azhar University, Boys, Cairo. Selection of patients according to inclusion criteria patients with myofascial pain, patients suffering from pain associated with disc displacement with or without reduction, patients suffering from pain associated with hypermobility of the TMJ and Patients with unilateral or bilateral disease were accepted equally. The exclusion criteria included if they never failed conventional therapy for TMD (e.g. bit appliance therapy, oral muscle relaxants, anti-inflammatory drugs, analgesics or physical therapy, pregnancy and lactation, taking aminoglycosides or curare-like compounds, history of neuromuscular disease such as Myasthenia Gravis and Epilepsy and local infection at the proposed site of injection, allergy to study medications. Patients were clinically assessed and divided into 2 groups:

Study group were injected with Botulinum toxin A while, control group were injected with plain saline. In each group bilateral masseters and temporalis muscles were injected, masseter muscles were injected in 5 spots and temporalis muscles in 3 spots.

Surgical Protocol

Pre-surgical preparation: Preoperative examination and patient's medical history was thoroughly checked and reviewed and the eligibility for the study was confirmed. 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. Patients were randomly distributed into 2 groups. Study group which include inject the masseter muscle and the lower border of temporalis muscle via 1 cc TB syringe and a 30-gauge needle the subject thus received 100 units of reconstituted botulinum toxin A35 units were injected into each masseter muscle and 15 units into each temporalis muscle. While, in control group the same sites of injection carried out as the study group. The only exception is that the subjects received unpreserved 0.9% sodium chloride instead of Botulinum toxin A.

Surgical Procedure

The intramuscular injections were performed with all patients awake in the clinic. The skin was cleansed with an alcohol swab. Then applied topical anesthesia at site of injection.

Study group: (Botulinum toxin A): Botox was supplied in 100-units vial stored at a temperature of -4c and was reconstituted right before injection was made to insure maximum efficacy. The vial was reconstituted with 2ml saline to obtain 5 units/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 and to ensure the vial integrity. The saline was not shaken to mix the toxin instead the vial was gently rolled back and forth between the palms. Masseter muscles were received 35 units and 15 units in temporalis in each muscle. 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. One more injection was given 1 cm inferior to the origin of the temporalis muscle.

Control group: 0.9% Sodium Chloride Injection: The same procedures were carried out as the study group but the subjects received unpreserved 0.9% sodium chloride instead of Botulinum toxin.

All patients 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 5 mm (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.

Some injections caused spot bleeding which was controlled easily with pressure. The important point was to stop leaking of the injected toxin. Figure 1.

Figure 1. Showing A) Acquired landmarks for injection; B) Injection of received subject in the origin of the masseter muscle; C) Injection of the body of the masseter muscle; D) Injection of the temporalis muscle.

Postoperative Care

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.

Ice pack applied immediately after injection to reduce postoperative pain, edema and erythema associated with the intramuscular injection.

Postoperative Clinical 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:

Subjective pain scores: Where based on visual analog scale (VAS), where 0 is no pain and 10 is the worst facial/jaw pain you had.

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.

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 to provide 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 with respect to discomfort expressed by the patient. (0) represented no discomfort on firm palpation and (3) severe discomfort with minimal pressure.

Masseter muscle activity: Muscle activity was measured 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.

RESULTS

The aim of this study was to evaluate injection of Botulinum toxin in masseter and temporalis muscles as a treatment modality for temporomandibular disorders pain. This study included 14 patients diagnosed with TMD. Postoperative evaluation include: Pain score, tenderness to palpation, range of motion and Electromyogram (EMG)* (Table 1).

Pain Score

In the first interval (1st-2nd visit), there was a percent increase in control group, in comparison to a decrease in Botox group. This difference was statistically significant (p = 0.00). In the second interval (2nd-3rd visit), there was a significantly greater decrease in Botox group (p = 0.004). In the 3rd interval (3rd-4th visit), there was a percent increase in control group, in comparison to a decrease in Botox group. This difference was statistically significant (p = 0.045). Overall (1st-4th visit), there was a percent increase in control group, in comparison to a decrease in botox group. This difference was statistically significant (p = 0.00).

Tenderness to Palpation

In the first interval (1st-2nd visit), there was a significantly greater percent decrease in Botox group (p = 0.00). In the second interval (2nd-3rd visit), there was a percent increase in control group, in comparison to a decrease in Botox group. This difference was statistically significant (p = 0.027). In the 3rd interval (3rd-4th visit), and Overall (1st-4th visit), there was a 100% percent decrease in Botox group, in comparison to -2.38% and - 16.67% in the control group respectively. This difference was statistically significant (p = 0.004, p = 0.001 respectively).

Table 1. Comparison of mean value of percent change of both groups at each interval (Mann Whitney U test).

		1st to 2nd visit		2nd to3rd visit		3rd to 4th visit		Overall (1st to 4th)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Pain score	Control	16.99	32.76	-8.37	21.94	7.82	13.25	6.31	28.11
	Botox	-58.50	19.68	-63.89	28.71	-12.50	20.00	-85.80	14.70
	P value	0.00*		0.004*		0.045*		0.00*	
Tenderness to palpation	Control	-2.38	27.94	4.76	9.34	-2.38	57.27	-16.67	36.00
	Botox	-76.19	23.29	-25.00	30.00	-100.0	.00	-100.0	.00
	P value	0.00*		0.027*		0.004*		0.001*	
Range of motion	Control	-.17	5.20	-1.78	4.73	3.01	4.55	.91	7.07
	Botox	16.59	7.87	5.67	3.11	3.22	5.05	27.05	9.64
	P value	0.001*		0.006*		0.937ns		0.00*	
EMG	Control	-4.08	5.40	4.53	5.86	2.17	4.96	2.13	4.20
	Botox	-47.90	20.23	-12.53	13.94	70.31	43.25	-29.55	10.26
	P value	0.001*		0.017*		0.006*		0.00*	

Significance level P ≤ 0.05, *significant, ns = non-significant.

Range of Motion

In the first interval (1st-2nd visit), there was a percent decrease in control group, in comparison to a percent increase in Botox group. This difference was statistically significant (p = 0.001). In the second interval (2nd-3rd visit), there was a percent decrease in control group, in comparison to an increase in Botox group. This difference was statistically significant (p = 0.006). In the 3rd interval (3rd-4th visit), a non-significantly greater increase was recorded in the Botox group (p = 0.937). Overall (1st-4th visit), there was a significantly greater percent increase in Botox group (p = 0.00).

EMG

In the first interval (1st-2nd visit), there was a significantly greater percent decrease in Botox group (p = 0.001). In the second interval (2nd-3rd visit), there was a percent increase in control group, in comparison to a decrease in Botox group. This difference was statistically significant (p = 0.017). In the 3rd interval (3rd-4th visit), there was a significantly greater percent increase in Botox group (p = 0.006). Overall (1st-4th visit), there was a percent decrease in Botox group, in comparison to a percent increase in control group. This difference was statistically significant (p = 0.00).

DISCUSSION

Temporomandibular disorders (TMDs) is a collective term, used to describe a group of conditions involving the TMJ, masticatory muscles and associated structures.[2]

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 mas-

ticatory musculoskeletal system.[17] Although TMD begins as functional muscular disorder, it ultimately can cause degenerative changes and internal derangement in the TMJ.[18]

Several studies concluded that females were more likely to have signs and symptoms of TMDs than males and are more likely to seek treatment.

Botulinum toxin A (BTX-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 innervates the affected portions of the muscle.[19] 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.[20] It 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,[21] strabismus, hemifacial spasm,[22] spasmodic torticollis,[23] oromandibular dystonia,[24] spasmodic dysphonia,[25] myofascial pain[26] temporomandibular dislocation[27] and temporomandibular disorders.[2,3,16,28] 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 Pruritus. There have been no reported cases of systemic toxicity in this study. Locally, diffusion of the toxin into adjacent muscular structures with their subsequent and inadvertent inhibition can occur.

Failure to achieve therapeutic muscular relaxation may be due to several causes. Insufficient 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.[29] The injection of BTX-A into the masseter and temporalis muscles of patients diagnosed with TMD yielded several significant findings. First is a reduction in both subjective pain (VAS) and tenderness in many patients. In all cases of pain reduction, the improvement was noted to coincide with the 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 events may be responsible for reducing the mechanical stimulation of sensitized peripheral nociceptive afferent pathways.[30]

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 overall 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 occur in the muscle as well as in the TMJ through reduced joint loading.[31]

All patients with restricted mouth opening experienced some degree of improvement in maximum range of vertical motion. This observation can be based on three possible mechanisms. 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.[20]

Inflammation of the muscles would tend to increase viscoelastic tone and therefore the stiffness of a muscle. Inflammation of the TMJ, particularly the capsule and supporting ligaments, also reduces the range of movement as in other injured joints.[32]

Most patients suggest that their limitation in jaw opening is secondary to pain centered around the jaw joints. It is likely that reduction in pain also helps increase range of motion. The tenderness to palpation scores also showed the most consistent improvement with time. The mechanism responsible for a reduction in pain in the injected muscles is not obvious, but the results clearly show that muscles treated with BTX-A are less tender to palpation.

Our results are also in accordance with those of Freund[2] who treated 46 TMD patients with BTX-A 150 U where both masseters 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. 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 pre-treatment assessment and the four follow-up assessments. 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.[33] The results of the present-day study go hand in hand with Shehryar [28] who treated 60 patients with chronic TMD (where 46 subjects had coexisting chronic tension-type headache). Subjects were followed on a monthly basis for 3 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.[28] 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 headache free days also improved post injection.[28] 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

According to this study we could concluded that:

1. Botulinum toxin A was safe and efficacious for the management

of patients with muscular TMDs and its effect extended 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 a well-defined definition for diagnosing the most common forms of TMDS.

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