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The Use of Botulinum Toxin for the Treatment of Temporomandibular Disorders: Preliminary Findings

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Purpose: The aim of this study was to evaluate the response of patients with temporomandibular disorders to Botulinum toxin A (BTX-A) therapy.

Methods: The 15 subjects enrolled in this uncontrolled study were diagnostically categorized and treated with 150 units of BTX-A. Both masseter muscles received 50 units each under eletromyographic (EMG) guidance. Similarly, both temporalis muscles were injected with 25 units each. Subjects were assessed at 2-week intervals for 8 weeks. Outcome measures included subjective pain by visual analog scale (VAS), measurement of bite force, interincisal opening, tenderness to palpation, and a functional index based on multiple VAS.

Results: All mean outcome measures, with the exception of bite force, showed a significant ($P = .05$) difference between the preinjection assessment and the four follow-up assessments. No side effects were reported.

Conclusions: BTX-A injections produced a statistically significant improvement in four of five measured outcomes, specifically pain, function, mouth opening, and tenderness. No statistically significant changes were found in mean maximum voluntary contraction or in paired correlation of factors such as age, sex, diagnosis, depression index, or time of onset.

Temporomandibular disorder (TMD) 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.[1-4] The role of occlusion remains uncertain.[5]

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. To improve on systemic muscle relaxants, a useful therapeutic agent would have to possess excellent specificity as well as a tolerable side effect profile. One such agent is the toxin produced by the gram-positive anaerobic spore-forming bacterium *Clostridium botulinum.*

A pilot study on the use of Botulinum toxin A (BTX-A) in TMD[6] has shown that BTX-A was effective in the treatment of some patients with TMD and that no significant side effects occurred. This preliminary report presents the results of the first 15 patients of this second, larger study investigating the response of patients with TMD to BTX-A therapy. Objective as well as subjective measures of outcome have been chosen that are significant to a patient's quality of life.

Patients and Methods

The study enrolled a total of 50 subjects, both male and female, between the ages of 16 and 75 years. Subjects were selected from a private practice and from the hospital oral surgery clinic. The study design was prospective and uncontrolled given that the pilot study[6] had shown a statistically significant clinical effect for BTX-A therapy.

On enrollment, each subject signed a consent, answered an extensive questionnaire, and was clinically assessed based on the Research Diagnostic Criteria (RDC) of Dworkin and LeResche,[7] with minor additions. Information gathered was used to profile patients demographically, historically, functionally,

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and psychologically and to document the physical findings. A "raw mean scale score" derived from the modified SCL-90-R Scales for depression and vegetative symptoms[7] was calculated for each subject. These scores allowed subjects to be descriptively classified as normal (score <0.535), moderately depressed (score 0.535 to <1.105), or severely depressed (score >1.105).

Subjects were diagnosed and assigned to one of three possible diagnostic categories:

Category 1: Only muscle or myofascial symptoms and findings
Category 2: In addition to the category 1 diagnosis, evidence of either internal derangement (such as clicking or deviation) or evidence of arthralgia such as tenderness on TMJ palpation
Category 3: Muscle pain, joint inflammation, and internal derangement

Patients with unilateral or bilateral disease were accepted equally. Patients with previously operated joints were also included. Subjects were excluded if they did not meet the diagnostic criteria for TMD as defined in the RDC or had never been treated with or never failed conventional therapy for TMD (eg, bite appliance therapy, oral muscle relaxants, anti-inflammatory drugs, analgesics, or physical therapy). Further exclusion criteria included a history of atopy or significant allergic reactions, and pregnancy or lactation.

The clinical method of administering the BTX-A was identical to that of the pilot study.[6] Both masseter and temporalis muscles were injected regardless of whether the disease was unilateral or bilateral. The masseters received 50 units each of BTX-A as Allergan BOTOX (Irvine, CA) divided evenly over five sites. All injections were percutaneous and intramuscular as verified by electromyographic (EMG) guidance. Similarly, the temporalis muscles were injected with 25 units each divided over five sites. The injection sites corresponded to areas of greatest muscle mass by palpation and greatest activity established via EMG, not necessarily corresponding to trigger points. Because it has been shown that task-dependent EMG-based heterogeneity exists in both the temporalis and massetter muscles,[8] resting muscle was used to determine areas of highest EMG activity.

Allergan BOTOX was reconstituted with saline as either a 10 unit/0.1 mL or 5 unit/0.1 mL solution just before injection as directed in the product insert. Subjects were offered sedation for the BTX-A injections via an intravenous route if they desired. The latter involved a combination of diazepam, fentanyl, and ketamine titrated intravenously to the desired effect. Most subjects chose to be injected only after the application of Astra EMLA (prilocaine-lidocaine) cream (Mississauga, Ontario, Canada) to the sides of the face 2 hours before treatment.

Outcome was based on five measures: subjective facial pain, orofacial function, interincisal opening, bite force or maximum voluntary contraction (MVC), and tenderness of the masticatory muscles. Assessments were carried out at 2-week intervals, bringing the total number of assessments (including the initial assessment) to five, for a total follow-up of 8 weeks. (Based on data from the pilot study,[6] the period of clinical effectiveness of the BTX-A therapy appeared to be approximately 6 weeks, with a mean onset time of 1 week.) Time points were referred to as '1' for the initial pre-injection assessment, '2' for week 2, '3' for week 4, and '4' for week 6, and '5' for week 8.

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

Subjective functional assessments were also based on a VAS. Subjects placed a mark on a line between '0', which indicated 'no limitation', and '10', which indicated 'extreme limitation'. A total of 10 additional VASs were averaged to produce a functional index. The scales represented chewing, drinking, exercising, eating hard food, eating soft food, smiling/laughing, cleaning teeth or face, yawning, swallowing, and talking.

The bite force analysis was done by having subjects apply pressure on a bite fork mechanism with the anterior teeth. The fork was 1 cm in width and covered with surgical rubber tubing to prevent tooth damage. Although it has been shown that maximum force can be generated at an interincisal opening between 14 and 28 mm,[9] a review of the study patient database showed that all patients opened at least 1 cm. Therefore the inter-fork distance was set at 1 cm. The bite fork apparatus was interfaced with a computer that sampled 20 times per second. The data were digitally normalized and converted to avoirdupois pounds to compensate for any nonlinearity in the mechanical apparatus. (Some studies report MVC in Newtons, where 4.45 N = 1 lb.) Subjects were instructed to bite as hard and as long as they were able. The maximum bite pressure achievable was recorded on initial assessment and at each follow-up.

Range of motion measurements were limited to maximum vertical mouth opening measured with a Boley gauge between the same upper and lower front tooth at each time. Tenderness was recorded in the temporalis, masseter, lateral pterygoid, sternocleidomastoid, and the TMJ capsule bilaterally. Reaction to pressure was graded from 0 to 3 with respect to discomfort expressed by the patient. A '0' represented no discomfort on firm palpation, and '3' represented severe discomfort with minimal pressure. A composite measure of tenderness of the face and neck was

reported at each assessment by adding the scores, with 30 being the maximum possible score.

Subjects were assessed at the same time of day at each follow-up by the same member of the investigative team. The treating clinician did not participate in the assessments. Patients were asked to refrain from any form of therapy related to TMD other than analgesics as necessary.

Results

Fifty-four subjects were referred for assessment; 39 were rejected based on the exclusion criteria. There were no subjects lost to follow-up. The mean age of the 15 subjects was 39 years (range, 16 to 75 years), with a female-to-male ratio of 13:2. The duration of TMD symptoms reported by subjects ranged from 6 to 242 months, with a mean duration of 124 months.

A correlation analysis of variable pairs showed no statistically significant relationships between depression, clinical diagnosis, time of onset of clinical weakness after BTX-A injection, age, sex, and duration of symptoms. Pain scores, composite function scores, vertical mouth opening, bite force, and composite tenderness scores at each of the five measurement times were averaged for each variable for the 15 subjects (Table 1). With the exception of bite force, each post-BTX-A treatment outcome measure showed a statistically significant ($P = .05$) difference from the preinjection value when subjected to a Duncan's multiple range test. None of the measures of a particular variable with respect to time showed any significant difference when the pretreatment measures were excluded.

The mean time of onset of subjective bite weakness was 8 days (SD = 1.7 days). An objective return to preinjection bite force was noted by the sixth week, although the other measures of treatment outcome remained statistically different through the eighth and final week of measurement.

Only two subjects requested and received intravenous sedation for the injections. No subjects reported a worsening of their condition after treatment (based on pretreatment measures), and no side effects were reported.

Discussion

The therapeutic use of BTX-A was first attempted in primates by Scott et al[10] in 1973. They subsequently reported its application in the treatment of strabismus in humans in 1980.[11] BTX-A has been shown to be effective in the treatment of blepharospasm,[12] strabismus,[13] hemifacial spasm,[14] spasmodic torticollis,[15] oromandibular dystonia,[16,17] and spasmodic dysphonia.[18] There is only one study that describes the use of BTX-A in the treatment of myofascial pain, the results of which were encouraging.[19]

Systemic side effects and local complications are uncommon with BTX-A. Systemic side effects are rarely reported, generally not dose related, and can include transient weakness, nausea, and pruritis.[20] There have been no reported cases of systemic toxicity (Allergan Botox product monograph). Locally, diffusion of the toxin into adjacent muscular structures, with their subsequent and inadvertent inhibition, can occur. An excellent and detailed review of the short- and long-term local and systemic effects of BTX-A injection has been prepared by Dutton.[21]

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.[22] It has been shown that deposition of BTX-A 0.5 cm from a motor end plate results in a 50% decrease in muscle fiber paralysis compared with the 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.[21]

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 some patients. This effect appears to be due to the BTX-A and not the "needling." In all cases of pain reduction, the improvement was noted to coincide with the objective and subjective weakening of the masticatory muscles and not before.

The possible mechanisms for these observations are speculative, but two known specific events occur: a reduction in the maximum contractile force of the

Table 1. CHANGES IN OUTCOME MEASURES WITH TIME

	Mean Pain (SD)	Mean Function Disability Index (SD)	Mean Opening MM (SD)	Mean Bite Force Lbs (SD)	Mean Tenderness (SD)
Preinjection	7.3 (2.0)	5.5 (1.7)	27 (11)	17 (8.8)	17 (5.6)
Week 2	5.5 (2.9)	4.1 (1.6)	33 (8.4)	14 (7.8)	7.5 (4.0)
Week 4	5.3 (2.9)	4.1 (2.1)	33 (8.0)	13 (7.2)	5.4 (6.0)
Week 6	4.1 (2.7)	3.8 (1.6)	34 (6.1)	17 (7.8)	5.6 (6.0)
Week 8	4.0 (3.1)	3.1 (2.1)	34 (5.5)	18 (6.5)	7.6 (9.2)

injected muscles (alpha motor neuron inhibition) and a reduction in the resting muscle tone (gamma efferent inhibition).[23] One or both of these events may be responsible for reducing the mechanical stimulation of sensitized peripheral nociceptive afferent pathways. Although Lund et al[24] concluded that there is no pain-mediated reflexive drive to increased muscle activity in TMD, there is some evidence suggesting that TMD patients engage in a more significant degree of schedule-induced oral habits.[25] By reducing the power and duration of effective contraction of the injected muscles, BTX-A also 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 as to reduce the stimulation of the 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. Although reversal of the muscular paralysis is due to muscle reinnervation[26] and not to the deinhibition of acetylcholine release, a transient direct effect of BTX-A on neuromodulator release is unlikely.

Those patients who did not respond subjectively with a reduction in pain may have suffered central neuroplastic changes to the degree that peripheral nociceptive input was no longer required to cause the perception of pain.[27,28] This is suggested by the observation that some patients showed no improvement in subjective pain on the VAS while showing marked improvement in pain to palpation. The depression and somatization scores of these patients did not correlate well with the subjective pain scores on the VAS. This implies a mechanism other than the affective state of a patient being responsible for the pain experience.

All patients with restricted mouth opening experienced some degree of improvement in maximal range of vertical motion. This observation can be based on three possible mechanisms: The first is muscular relaxation. Given the reduced tone of the flexor muscles secondary to the inhibition of both gamma and alpha neurons, it would be expected that increased stretch of these muscles could be achieved. The second mechanism is based on a reduction of inflammation both within the muscle and within the TMJ. Inflammation of the muscle fascicles would tend to increase the viscoelastic tone and therefore the stiffness of a muscle.[27] Inflammation of the TMJ, particularly the capsule and supporting ligaments, also reduces the range of motion, as is experienced in other injured joints. The third mechanism is the guarding response to pain. Most patients suggest that their limitation in jaw opening is secondary to pain centered around the jaw joints. It is likely that all three mechanisms contribute to the decrease in jaw mobility seen in TMD. The improvement in pain scores on joint capsule palpation noted after BTX-A injection of the muscles suggests that indirect reduction in joint inflammation is a major factor responsible for the increase noted in maximal mouth opening.

Bite force or MVC measurements showed a trend toward decreased force during the middle periods. When the individual data were examined, some subjects showed a paradoxical response to the BTX-A injections, with increased MVC and decreased subjective weakness. As expected, in most subjects the injection of BTX-A into the flexor muscles produced subjective as well as objective (MVC) reductions in power. The paradoxical response in some appears to be due to the significant joint tenderness present in these patients before injection. Their initial MVC was so low that with the reduction in joint pain noted on palpation on follow-up, (presumably due to reduced joint inflammation), their MVC increased. The increased values in this group reached the same range as the decreased values in the nonparadoxical group. This implies that all patients probably develop muscular weakness, but that in one group the initial muscle power (MCV) was masked by the joint pain. It is clear that the lack of statistical significance in postinjection patients with respect to bite force is due to the divergent responses.

The composite tenderness scores, likely the most susceptible to examiner subjectivity, 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 BTX-A–treated muscles are less tender. The temporal relationship between the decrease in mechanically induced pain appreciation in the flexor muscles and the onset of relaxation (subjective weakness and decreased MVC) implies an indirect effect of BTX-A on nociception.

A final observation noted in the study was that all patients improved in their functional index scores. Although the index is a composite of both closing functions such as chewing and opening functions such as yawning, the overall index improvement shows that pain experience rather then muscular weakness is more responsible for functional disability.

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Discussion

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In the 1980s botulinum toxin was introduced as treatment for dystonic disorders affecting the extraocular muscles (eg, strabismus and blepharospasm). The US Food and Drug Administration approved it specifically for application in these disorders and the typical doses used are in the 10 to 15 unit range, a dose range that is an order of magnitude below the doses described in this study by Freund et al. The accepted mechanism of action for botulinum toxin is that it produces a blockade of neuromuscular transmission thereby preventing the release of acetylcholine. Without release of this neurotransmitter, affected terminals will not produce muscle contraction. The nature of this blockade is long-lasting, but not permanent. After a period of time, the blocked nerves develop sprouts that re-establish a new neuromuscular junction.

Certainly, from reading the literature, it is evident that botulinum toxin is used for purposes other than blocking extraocular muscle contraction. These "off-label" uses of botulinum toxin generally involve disorders that have involuntary motor activation as a central feature of the patient's