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Botulinum toxin: new treatment for temporomandibular disorders

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SUMMARY. Background: 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. In this study, we evaluated subjective and objective responses to treatment with botulinum toxin A (BTX-A) in a group of 46 patients with TMDs. *Methods*: 46 subjects with TMD were enrolled in this uncontrolled study and treated with BTX-A 150U. Both masseter muscles were injected with 50 U each and both temporalis muscles with 25 U each under electromyographic guidance. Subjects were assessed at two-week intervals for eight weeks. Outcome measures included subjective assessment of pain by visual analogue scale (VAS), measurement of mean maximum voluntary contraction (MVC), interincisal oral opening, tenderness to palpation, and a functional index based on multiple VAS. Medians of the data were taken for each outcome measure at each time point and subjected to Duncan's multiple range test. *Results*: There were significant ($P<0.05$) differences in all median outcome measures between the pre-treatment assessment and the four follow-up assessments except for MVC. Although MVC was significantly reduced midway through the study, it had returned to pretreatment values by the final two assessments. All other outcome measures remained significantly different from the pretreatment findings. Paired correlation of variables including age, sex, diagnosis, depression index, and time of onset showed no significant differences. *Conclusions*: BTX-A injections produced significant improvements in pain, function, mouth opening, and tenderness to palpation. MVC initially diminished then returned to the initial values. Although the study was uncontrolled, the results strongly suggest that BTX-A reduces severity of symptoms and improves functional abilities for patients with TMD and that these extend beyond its muscle-relaxing effects. © 2000 The British Association of Oral and Maxillofacial Surgeons

INTRODUCTION

Temporomandibular disorder (TMD) is a collective term used to describe a group of conditions involving the temporomandibular joint (TMJ), masticatory muscles, and associated structures. The incidence in North America is about 10%,[1,2] and it often presents as pain and dysfunction specific to the jaws; associated complaints can include earache, headache, neck pain, and facial swelling.

TMD is different from other pain that produces spastic conditions of the head and neck such as torticollis or oromandibular dystonia. The clinical picture more closely parallels complex joint-related conditions such as cervicogenic headaches and chronic low back pain. As in most musculoskeletal conditions, treatment includes drugs such as narcotic analgesics, anti-inflammatory agents, and muscle relaxants. Physical treatments such as orthotic devices, physiotherapy, massage, acupuncture, and others are also often used. Surgical interventions such as arthrocentesis, arthroscopy, and open arthrotomy are indicated in specific circumstances. None of these treatments has proved to be wholly or consistently effective, and some are associated with appreciable undesirable side-effects. It is estimated that three-quarters of patients with severe chronic facial pain who are being treated with opioids do not achieve a reduction in pain or improvement in function.[3,4]

Directing treatment at the muscular component of TMD, which in some patients can be identified as non-spastic clenching or bruxism, could yield important therapeutic gains. To improve on systemic muscle relaxants currently used, a useful, new therapeutic agent would have to possess high specificity as well as tolerable side-effects.

Botulinum toxin A (BTX-A) is one such agent and it has been shown to be effective in the treatment of some patients with TMD.[5] Here, we present the results of a larger study in which we investigated the response of patients with TMD to BTX-A.

PATIENTS AND METHODS

We enrolled a total of 50 men and women between the ages of 16 and 75 years in the study. Subjects were recruited from the public at large and from a private practice. The study design was prospective and the results were compared with baseline values obtained before the start of treatment. A limited pilot study[5] shown that BTX-A had significantly helped patients under the same conditions. Both objective and subjective measures of outcome were chosen that have an appreciable effect on a patient's quality of life.

On enrollment, each subject gave informed consent, answered an extensive questionnaire, and was clinically assessed using the research diagnostic criteria described by LeResche *et al*,[6] with minor additions. Information gathered was used to characterize

patients (demographically, historically, functionally, 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 was calculated for each subject.[6] 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: myofascial symptoms and signs alone; myofascial symptoms with either internal joint derangements or arthralgia; and myofascial symptoms with internal joint derangement and arthralgia.

Patients with unilateral or bilateral disease were included. Patients whose joints had previously been operated on were also included. Subjects were excluded if they did not meet the diagnostic criteria for TMD as defined in the research diagnostic criteria, or had never been given or never failed to respond to conventional treatment (such as bite appliances, oral muscle relaxants, anti-inflammatory drugs, analgesics, or physiotherapy). Further exclusion criteria included a history of atopy or allergic reactions, and pregnancy or lactation.

The method of giving BTX-A was identical to that of the pilot study.[5] Both masseter and temporalis muscles were injected regardless of whether the disease was unilateral or bilateral. BTX-A as Allergan BOTOX® 50 U was injected into each masseter, divided evenly over five sites. All injections were percutaneous and intramuscular as verified by electromyographic (EMG) guidance. The temporalis muscles were similarly injected with 25 U each divided over five sites. The injection sites corresponded to areas of greatest muscle mass on palpation, and greatest activity established by EMG, not necessarily corresponding to trigger points. Because there is task-dependent EMG-based heterogeneity in both the temporalis and masseter muscles,[7] for consistency, resting muscle was used to find the 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 by the manufacturer. Subjects were offered intravenous sedation for the BTX-A injections if they desired. This comprised a combination of diazepam, fentanyl, and ketamine titrated to give the desired effect. Thirty-eight of the 46 subjects declined sedation after the application of prilocaine – lignocaine eutectic cream (Emla, Astra Pharmaceuticals) to the sides of the face two hours before treatment.

Five outcome measures were used: subjectively judged facial pain, orofacial function, inter-incisal opening, bite force, or maximum voluntary contraction (MVC), and tenderness to palpation of the masticatory muscles.

Assessments were carried out at two-weekly intervals, bringing the total number of assessments (including the initial assessment) to five, for a total study length of eight weeks. (Based on data from the pilot study,[5] the period of clinical effectiveness of BTX-A as a masticatory muscle relaxant seemed to be roughly six weeks, with a mean onset of 1 week.)

Subjective pain scores were assessed on a visual analogue scale (VAS) where 0 is no pain and 10 is 'the worst facial or jaw pain you have had'.

Subjective functional assessments were also assessed by a VAS. Subjects placed a mark on a line between 0, which indicated 'no limitation', and 10, which indicated 'extreme limitation'. A median of 10 additional VAS was calculated to produce a functional index. The scales were for chewing, drinking, exercising, eating hard food, eating soft food, smiling or laughing, cleaning the teeth or face, yawning, swallowing, and talking.

The bite force was analysed by asking subjects to apply pressure to a bite fork mechanism with the anterior teeth. The fork was 1 cm wide and covered with rubber surgical 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,[8] a review of the study database showed that all patients could open their mouths at least 1 cm. The interfork distance was therefore set at 1 cm. The bite fork apparatus was interfaced with a computer that took 20 samples/second. The data were normalized digitally and converted to avoirdupois pounds to compensate for any non-linearity in the mechanical apparatus. (Some studies report MVC in N, 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.

Measurements of range of motion were limited to maximum vertical opening measured with a Boley gauge between the same upper and lower front tooth at each time point.

Objective tenderness to palpation was recorded in the temporalis, masseter, lateral pterygoid, sternocleidomastoid, and the TMJ capsule bilaterally. Reaction to pressure was graded from 0 to 3 depending on the discomfort expressed by the patient. 0 indicated no discomfort on firm palpation and 3 severe discomfort with minimal pressure. A composite objective measure of tenderness to palpation 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 team. The treating clinician did not participate in the assessments. Patients were asked to stop any treatment for their TMD except analgesics as necessary, for the course of the study.

RESULTS

Seventy-one subjects were referred for assessment and 21 were rejected based on the exclusion criteria. Four subjects were lost to follow-up (two moved and two refused to return for personal reasons). The mean age of the 46 subjects was 40.5 years (range 16–75) with a female: male ratio of 5.6:1. The duration of symptoms of TMD ranged from 6–410 months, with a median duration of 96 months.

Table 1 – Median (range) outcome values at each time point (*n* = 46 in each case)

	Before injection	2 weeks post injection	4 weeks post injection	6 weeks post injection	8 weeks post injection
VAS pain score	8 (3–10)	6 (1–9)	5 (0–9)	5 (0–10)	5 (0–9)
Function Disability Index	5.3 (1–9)	4.4 (0.6–9)	4.1 (1–9)	4.1 (0.5–9)	3.9 (0.6–9.5)
Opening of jaw (mm)	29.5 (12–54)	33.5 (12–55)	33 (14–50)	33 (16–50)	34.5 (18–53)
Bite force (lb)	12 (1–37)	9 (1–27)	11 (1–28)	11 (0–30)	14 (1–37)
Tenderness to palpation score	15.5 (5–30)	8 (1–30)	6 (0–24)	4.5 (0–26)	6 (0–30)

A correlation analysis of variable pairs found no significant relationships between depression, clinical diagnosis, time of onset of clinical weakness after BTX-A injection, age, sex; or duration of symptoms. There was an inverse trend between increasing age and degree of improvement in outcome measures. Median pain scores, composite function scores, vertical opening, bite force, and composite tenderness to palpation scores were calculated for each of the five measurement times for each variable for the 46 subjects (Table 1). All assessed values within an outcome measure were subjected to a Duncan's multiple range test. This showed that there were significant ($P<0.05$) differences between the pre-treatment values and all post-treatment values except MVC. As expected, MVC was significantly lower after BTX-A injection but then returned to pre-injection values by the eighth week.

The median time of onset of subjective bite weakness was 9 days (SD = 2.2 days).

No subjects reported a worsening of their condition after treatment (based on pretreatment measures) and no side-effects were reported.

DISCUSSION

Botulinum toxin A, one of seven subtypes, is a potent biological toxin produced by *Clostridium botulinum*.[9] BTX-A is a pre-synaptic neurotoxin[10] which causes dose-dependent weakness or paralysis in skeletal muscle by blocking the calcium-mediated release of acetylcholine from motor nerve endings.[11] This functionally denervates the affected portions of the muscle. The primary effect is on α motor neuron function but may also affect the γ motor neurons in the muscle spindles, and lower resting tone.[12] Local paralysis is reversed chiefly by neural sprouting with re-innervation of the muscle[13] and function is restored in two to four months. No other physiological function has been assigned to BTX-A so far.

BTX-A has been used extensively in the treatment of blepharospasm,[14,15] strabismus,[16,17] hemifacial spasm,[18,19] spasmodic torticollis,[20,21] oromandibular dystonia,[22,23] and spasmodic dysphonia.[19] We know of only one study that describes its use in the treatment of myofascial pain, the results of which were encouraging but did not show a significant improvement.[24]

Systemic side-effects with BTX-A are uncommon but can include transient weakness, nausea, and pruritis.[20] The toxin may diffuse locally into adjacent muscular structures, causing subsequent and inadvertent inhibition. An excellent and detailed review of the short-and long-term, local and systemic effects of BTX-A injection has been prepared by Dutton.[25]

Muscular relaxation may fail for several reasons including insufficient concentration of active toxin in the vicinity of the motor end plate,[26] the presence of antibodies to BTX-A, or improper reconstitution and storage of the drug.[25]

The dysfunction associated with TMD is usually caused by pain from both articular sources and myofascial structures. In the case of articular pain, inflammation of the associated tissues limits the range of movement as well as causing discomfort with loading, reflected in an inability to chew and pain on mouth opening. The source of chronic myofascial pain is not clear.[27,28] It is also not clear whether chronic myofascial TMD pain is related to other symptomatically similar conditions such as fibromyalgia.[28] There is some consensus that both peripheral and central mechanisms are variably involved in the propagation of pain in TMD.[29] It has been suggested that hypoxic peripheral mechanisms evoke myofascial TMD pain secondary to electrically silent local muscular contractures.[30,31] Centrally, chronic neuroplastic changes alter the size and sensitivity of receptor fields to stimulation.[31–33] Neuropeptides such as substance P and N-methyl-D-aspartate (NMDA) have been implicated in the induction of neuroplastic changes.[34–37] Although it has not been specifically studied as yet, there is no evidence that BTX-A alters neuropeptide concentrations centrally despite its uptake into the central nervous system.[38,39] Any moderating effect on TMD pain and dysfunction therefore needs to be elucidated in terms of its inhibition of muscle activity which, although peripheral to central neural activity, may be altered as a secondary consequence of the primary action of the drug.

The injection of BTX-A into the masseter and temporalis muscles of the study group caused a reduction in subjective pain (VAS) in 40 of 46 subjects (87%) and

a reduction in objective pain (tenderness to palpation) in 44 of 46 subjects (96%). In all cases the improvement coincided with the objective and subjective weakening of the masticatory muscles and not before. Based on this temporal relationship therefore, it is reasonable to assume that the clinical changes are caused by BTX-A and not by the 'needling'.

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 efferents resulting in a reduction in the resting muscle tone.[12]

One or both of these events may be responsible for reducing the mechanical stimulation of sensitized peripheral nociceptive afferent pathways. Unlike pathological bruxing or oromandibular dystonia, the muscular activity in TMD can be more subtle. There is evidence that patients with TMD may have more schedule-induced oral habits,[40] 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 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. As reversal of the muscular paralysis is by re-innervation of the muscle[13] and not the de-inhibition of ACh 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 had central neuroplastic changes to the degree that peripheral nociceptive input was no longer required to perceive pain.[31,32] This is suggested by the observation that some patients showed no improvement in subjectively judged pain on the VAS but had much less pain on palpation. The depression and somatization scores of these patients did not correlate well with the subjective pain scores. This implies a mechanism responsible for the pain experience other than the affective state of a patient.

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 γ and α neurons, it would be expected that these muscles could be stretched further. 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.[31] Inflammation of the TMJ, particularly the capsule and supporting ligaments, also reduces the range of movement as 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

centred around the jaw joints. It is likely that all three mechanisms contribute to the reduction in jaw mobility seen in TMD. The improvement in pain scores on palpation of the joint capsule noted after BTX-A injection of the muscles suggests that indirect reduction in joint inflammation is a main factor in the increase in maximal opening.

Measurements of bite force or maximum voluntary contraction (MVC) showed a trend towards reduced force during the middle time periods. When the individual data were examined, some subjects had a paradoxical response to the BTX-A injections, with increased MVC and reduced 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 seems to result from the appreciable joint tenderness present in these patients *before treatment*. Their initial MVC was so low that with the improvement in joint pain noted on palpation on follow-up (presumably as a result of reduced joint inflammation) their MVC increased. The increased values in this group reached the same range as the decreased values in the non-paradoxical group. This subset also had a trend towards greater improvement in joint pain on palpation at follow-up, again presumably as a result of reduced joint inflammation. This implies that all patients probably develop muscular weakness, but that in one group the initial muscle power (MCV) was moderated by the joint pain on loading.

The composite tenderness to palpation scores, which are probably 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 muscles treated with BTX-A are less tender to palpation. The temporal relationship (Fig. 1) between the reduction in mechanically induced pain appreciation in the flexor
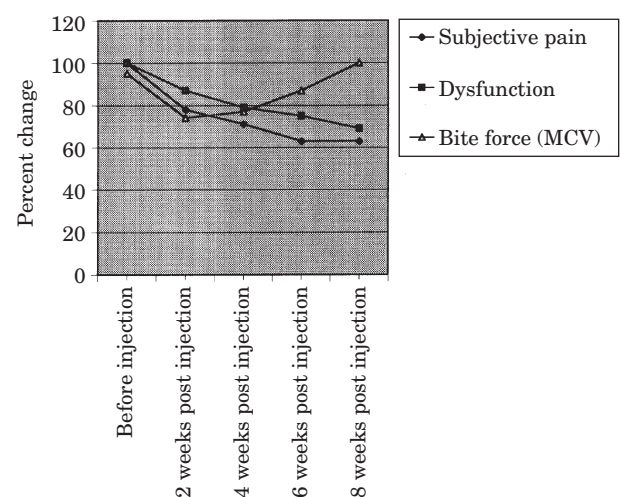

Fig. 1 – Relative change in pain, dysfunction and bite force with time.

muscles and the onset of relaxation (subjective weakness and decreased MVC) implies an indirect effect of BTX-A on nociception.

A final observation in the study was that most patients (40 of 46 subjects, 87%) had improved functional index scores. Figure 1 provides a chronological comparison of muscle weakness, pain relief, and functional index scores. As expected, the onset of muscle weakness is delayed commensurate with the pharmacological action of BTX-A. Pain relief closely follows the muscular effect at onset but, importantly, persists beyond the loss of muscle weakness. Comparably, functional index scores parallel pain and also persist beyond the return to normal muscle activity. This observation implies that pain relief, rather than muscular weakness, is more responsible for the improvement in functional ability.

The findings in this study also pose a number of questions about the role the 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 the 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.

Acknowledgements

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