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Randomized controlled trial of botulinum toxin A for chronic myogenous orofacial pain

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Abstract

The purpose of this study was to determine whether botulinum toxin A (BTX-A) was efficacious for the treatment of chronic moderate to severe jaw muscle pain in females. This was a randomized double-blind, placebo-controlled crossover trial of BTX-A. Twenty five units injected into each temporalis muscle and 50 U injected into each masseter muscle using three sites per muscle with 0.2 cm^3 per site. Data were collected at baseline, 8, 16, 24 weeks, with crossover occurring at 16 weeks. Primary outcome variables were pain intensity and unpleasantness, measured by horizontal visual analog scale (VAS). Secondary outcome variables were maximum interincisal opening without and irrespective of pain, muscle palpation tenderness (12 points), and four general questions. Fifteen female patients were enrolled (18–45 years), but only ten completed the trial. Of those who finished, no statistically significant difference was found in pain intensity ($P = 0.10$), unpleasantness ($P = 0.40$), palpation muscle tenderness ($P = 0.91$), or the three general questions ($P = 0.64$, $P = 0.66$, $P = 0.67$). Statistical significance was achieved for maximum opening without pain ($P = 0.02$) and irrespective of pain ($P = 0.005$) with the BTX-A arm having a relative decreased opening. No statistically significant difference was observed in any outcome measures except maximum opening, which showed BTX-A patient opening less wide than placebo. The results do not support the use of BTX-A in the treatment of moderate to severe jaw muscle pain in this patient population.

Keywords: Pain; Intractable; Facial pain; Botulinum toxins; Women; Masticatory muscles; Randomized controlled trials

1. Introduction

There has been a lot of interest in the use of botulinum toxin for a wide range of muscle-based disorders. Within the literature, the reported use was to selectively paralyze muscle that normally complicates healing and recovery; control of gait disorders; treat achalasia, anismus, stuttering, and spastic bladder; reduce inappropriate muscle contractions; control migraine headaches; treat chronic pain; and enhance cosmetic appearance (NIH, 1991; Jankovic and Brin, 1997; Silberstein et al., 2000). Botulinum toxin A (BTX-A) has become the 'treatment of choice' for certain centrally mediated movement disorders, such as blepharospasm (NIH, 1991). In recent years, the use of BTX-A has been reported to reduce muscle pain (Moore and Blumhardt, 1991; Raj, 1997) and some practitioners have advocated its use for muscular pain management (Wheeler et al., 1998; Childers et al., 1998; Porta et al., 1998). Two review articles investigated whether BTX-A decreases pain associated with undesired muscular contractions and presented compelling evidence that pain was markedly reduced when involuntarily muscle activity was reduced (Raj, 1997; Childers et al., 1998).

Muscle pain without overt muscle spasm/hyperactivity has also received some research attention. One randomized controlled trial investigated BTX-A efficacy in patients with fibromyalgia, but was stopped because of adverse effects without reduction in pain in the BTX-A group (Paulson and Gill, 1996). BTX-A to treat pain of myofascial origin was used on two patients who responded positively with injections, albeit minimally (Acquadro and Borodic, 1994). Another open-label study also reported favorable results in 52 patients (Alo et al., 1997). Three controlled studies with BTX-A treatment have investigated various muscle groups, with varying degrees of success (Cheshire et al., 1994; Wheeler et al., 1998; Porta, 2000). A recently published trial, testing BTX-A against placebo in a blinded

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fashion, found no difference between the two treatment modalities (Wheeler et al., 2001).

The use of BTX-A for myogenous orofacial pain has been reported three times by the same group (Freund and Schwartz, 1998; Freund et al., 1999, 2000). All reports were open-labeled trials of a heterogeneous patient population. There was no report of any untoward side effects with treatment, except for the decrease in bite force as measured during their studies.

The purpose of this study was to determine whether the application of BTX-A to the masseter and temporalis muscles of patients with chronic myogenous orofacial pain reduces pain and increases function.

2. Subjects and methods

Bioethical approval was sought and granted at our institution. This study was a prospective, randomized, double-blind, placebo-controlled, crossover clinical trial at a single center. Only female patients between the age 18 and 45 years were recruited by newspaper advertisement for patients with temporomandibular disorders (TMD) or painful temporomandibular joint (TMJ) symptoms. They had to report chronic ($\geq$6 months duration) pain in the muscles of mastication (presentation in the temporalis and masseter muscles) that was of moderate to severe intensity ($\geq$50 mm on a 100 mm VAS). This is consistent with the Research Diagnostic Criteria for Temporomandibular Disorders, Group I.a. and II.b, or myofascial pain without and with limited opening (Dworkin and LeResche, 1992).

Women who had inflammatory temporomandibular joint pathology, determined by joint palpation at rest and during function, were excluded. This effectively addressed any symptomatic temporomandibular joint disc displacements and arthralgias (Groups II and III of the TMD Research Diagnostic Criteria) without making use of advanced imaging (Dworkin and LeResche, 1992). It was felt that magnetic resonance imaging of the temporomandibular joint, to determine disc position, would be of no diagnostic benefit when joint palpation is pain-free, since up to one-third of the general asymptomatic population has disc displacement (Katzberg et al., 1996; Tasaki et al., 1996). Subjects with dental decay or intraoral soft tissue lesions, who were taking regular opioid analgesics, who had a history of temporomandibular joint surgery or trauma were also excluded.

Due to possible interactions with BTX-A or its delivery, women who were lactating, pregnant or planning pregnancy, taking aminoglycoside antibiotics, anticholinesterases and non-depolarizing or depolarizing muscle relaxants, or who had a neurological or bleeding disorder were excluded. To ensure that the outcome was not confounded by other interventions, subjects could not initiate or change medicinal or physical therapies during the trial. A minimum of 1 month lead in period was required prior to initiation of the study.

The most variable measure was thought to be the point of maximal pain free opening (Goulet et al., 1998). Power analysis revealed that 25 patients would be required to detect a clinically significant change (6 mm interincisal increase), when $\alpha = 0.05$ and $\beta = 0.10$. Therefore 15 crossed patients was the target enrollment number, allowing for a conservative dropout rate. The plan was to recruit more patients, after the completion of the initial study, if additional power was required.

During the first appointment, prospective patients had the research trial explained to them and were screened for trial suitability. If they fulfilled the criteria and wished to proceed, consent was obtained and baseline data were collected. Patients were randomly assigned to one of the two different treatment groups by a computer-generated sequence prior to enrollment. The next appointment, within 1 week, was the injection of either drug in a double-blinded fashion. BTX-A (Botox by Allergan, Markham ON, Canada) and placebo (0.9% normal saline) were prepared according to the manufacturer's recommendations by our institution's research pharmacist. A total volume of 0.2 cm^3 was injected three times into each temporalis and masseter muscle (Fig. 1). These muscles were chosen since they were symptomatic. The medial pterygoid muscles were not injected to eliminate the possibility of total paralysis of all jaw elevating muscles, thus rendering the patients unable to close their mouth. The lateral pterygoid muscles were not injected since they oppose the jaw elevators and function to open the jaw. Also, this protocol is in accordance with other previously reported trials, which treated only the temporalis and masseter muscle groups and reported moderate to good success in reducing pain (Freund and Schwartz, 1998; Freund et al., 1999, 2000).

A 27 gauge, Teflon-coated needle (King Medical, King City, ON, Canada) attached to an audioamplified electromyographic (EMG) machine (Allergan, Markham ON, Canada) was used to confirm placement within the appropriate muscle and deliver the drug. The anatomical landmarks were determined with palpation during clenching and the correct needle tip placement was determined by first feeling for the 'pop' when inserting the needle through fascial planes and then by positive EMG activity with clenching and no EMG activity at rest. No topical, local or general anesthesia was administered prior, during or after injection. Twenty five units of 0.6 cm^3 was divided evenly over the three injection sites of each temporalis muscle and 50 U of 0.6 cm^3 was divided evenly over the three injection sites of each masseter muscle.

Outcome measurements were obtained at baseline and at 8 weeks, which was deemed to when therapeutic effect would reliably occur. This allowed for approximately 7 weeks of muscle paralyzation and desensitization, up to approximately 1 week for onset time, and was well before loss of clinical activity due to axonal sprouting and renervation, occurring at 12 weeks postinjection (Freund and Schwartz, 1998; Göbel et al., 2001). Crossover occurred at

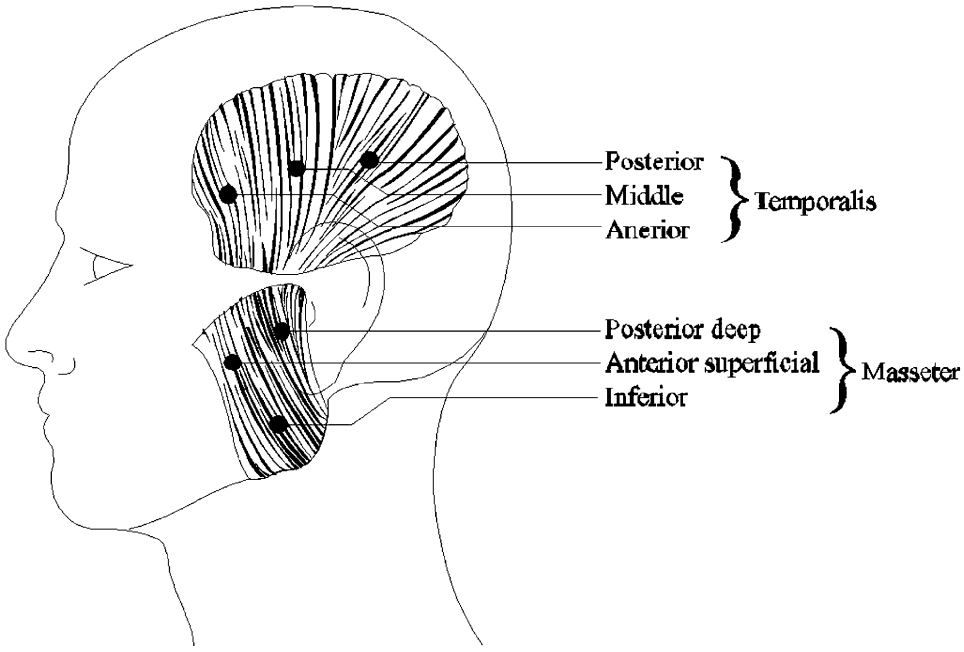

Fig. 1. Palpation and injection points of the muscles of mastication.

16 weeks, allowing for 4 weeks of washout, and comprised the baseline value for the crossed-over arm.

The primary variable was pain, which was recorded on a left to right horizontal VAS, with 0 mm being no pain and 100 mm being the worst pain the patient could possibly imagine. Patients were asked to rate both their average pain intensity and pain unpleasantness over the previous week (Carlsson, 1983; Price et al., 1983). A positive treatment response was defined as a decrease in VAS of 20 mm or more (Farrar et al., 2001).

Voluntary range of interincisal jaw opening without pain and irrespective of pain was measured in millimeters. A positive treatment response was defined as an increase in opening of 6 mm or greater (Goulet et al., 1998).

Palpation tenderness, expressed as either a Yes or No response for each of the 12 predetermined sites; temporalis (anterior, middle, posterior), and masseter (posterior deep, anterior superficial, inferior) was recorded (Fricton et al., 1988) (Fig. 1). These sites corresponded to the injection sites. Normative values at each of the specific sites for females have been previously reported (Chung et al., 1992) and a positive response was defined as pain being perceived one standard deviation below the pain threshold of normal healthy volunteers. The cut off values used for muscle tenderness in the present study were; anterior temporalis (1.84 kg/cm^2), middle temporalis (2.18 kg/cm^2), posterior temporalis (2.26 kg/cm^2), posterior deep masseter (1.54 kg/cm^2), anterior superficial masseter (1.51 kg/cm^2) and inferior masseter (1.41 kg/cm^2). A single algometer (GNR Orthopaedic and Rehabilitation Products, Ocala FL, USA) was used. This algometer had a circular rubber tip with a diameter of 1 cm and was applied at a rate of 0.4 kg/cm^2/s (Fischer, 1987; Chung et al., 1992; Goulet et al., 1998). The end point of pressure application was either reaching the estimated pain threshold level or when the patient gave a positive response of pain.

Breakthrough analgesic medication, 500 mg of acetaminophen (Tylenol ES, McNeil Pharmaceuticals, Guelph ON, Canada), was provided. Each patient was asked not to supplement with other analgesics.

The following four general subjective questions were asked at the beginning of each follow-up evaluation:

(i) Were the injections painful? (yes/no)
(ii) Is treatment worth the trouble (pain, risk, time, potential cost)? (yes/no)
(iii) Would you recommend treatment to a friend/family member with the same condition? (yes/no)
(iv) What adverse effects did you experience? (open-ended answer)

2.1. Statistical analysis

The change from baseline to 8 weeks for both groups, BTX-A and placebo, were compared using a two-tailed paired *t*-test for most variables. The data were analyzed using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA) and included only the patients who completed both arms of the crossover trial. Carryover effect was investigated by using a two-tailed paired *t*-test. The testable general questions, first three (Yes/No) were compared using logistic regression with crossover design. This data was analyzed using SAS 8.01 for Windows (SAS Institute

Table 1
Patient demographics of the 15 Caucasian women at time of inclusion into study

Age (years)	33 (mean)	18–45 (range)
Education (obtained greater than high school)	10	
Employment status (employed)	12	
Litigation pending (yes)	2	
VAS intensity (0–100 mm)	56 (mean)	30–73 (range)
VAS unpleasantness (0–100 mm)	61 (mean)	30–99 (range)
Duration of pain (months)	98 (mean)	12–246 (range)
Jaw opening without pain (mm)	26 (mean)	11–46 (range)
Maximum jaw opening (mm)	43 (mean)	27–56 (range)
Number of tender points (12 maximum)	9 (mean)	4–12 (range)

Inc., Cary, NC, USA) and again, included only the patients who completed both arms of the crossover trial. Significance for all statistics was regarded as $P < 0.05$.

3. Results

A total of 34 women were evaluated for study suitability after initial telephone screening. Fifteen patients, who happened to be of Caucasian descent, entered the study (Table 1). Only ten patients completed the entire study, while five dropped out (Table 2). Three patients experienced an escalation of their pain and started taking analgesics prohibited by study design. The first patient, who received placebo, dropped out during the first arm before the first evaluation at 8 weeks because she experienced increased pain and started taking opioid analgesics. The second patient, who received placebo, dropped out during the first arm before the 16-week evaluation because she started taking non-steroidal anti-inflammatory drug (NSAID) analgesics for escalating pain. The third patient, who received BTX-A, dropped out during the first arm before the 16-week evaluation because she started taking opioid and NSAID analgesics for escalating pain. Her pain and headaches had increased since the day of the injections and this pain had not subsided. The other two patients experienced unilateral zygomaticus major paralysis with injections and both had received BTX-A. They both dropped out during the first arm, one before and one after the 16-week evaluation, and had also experienced lingering pain with injections. Neither patient wanted to subject themselves to another 12 injections and chose not to continue.

The two primary variables were pain intensity and pain unpleasantness, measured as the difference between baseline and 8 weeks in millimeters by VAS. No significant difference was observed between the two groups for pain intensity ($P = 0.10$). The mean change was a 19 mm reduction in pain intensity (SD = 31) for the BTX-A group and a 1 mm reduction for the placebo group (SD = 16). No significant difference was observed between the two groups for pain unpleasantness ($P = 0.40$). The mean change was a 13 mm reduction in pain unpleasantness (SD = 23) for the BTX-A group and a 5 mm reduction for the placebo group (SD = 16). The order of treatment provided had no effect on either pain intensity ($P = 0.32$) or pain unpleasantness ($P = 0.35$). Patients who had a favorable response to BTX-A in both pain intensity and unpleasantness scales are charted in the upper right-hand quadrant of Fig. 2. Four patients improved with a clinically significant magnitude, a 20 mm reduction in pain, in at least one scale without worsening in the other. Five patients had no clinically significant effect and one patient worsened in both pain intensity and unpleasantness scales.

The secondary variables of maximum opening without pain and irrespective of pain both revealed a statistically significant change. The maximum opening without pain improved by 10 mm (SD = 9) in the placebo group, but remained the same 0 mm (SD = 11) with BTX-A ($P = 0.02$). The maximum opening irrespective of pain improved by 5 mm (SD = 7) in the placebo group, but worsened by 3 mm (SD = 5) in the BTX-A group ($P = 0.005$). No carry over effect was found for either maximum opening without pain ($P = 0.33$) or maximum opening irrespective of pain ($P = 0.61$).

The number of muscular tender points before and after treatment is shown in Table 3 and did not significantly differ between treatment groups ($P = 0.91$). The response to the general questions is shown in Table 4 and did not significantly differ between groups for all three testable general questions, 'Were the injections painful?' ($P = 0.64$), 'Is treatment worth the trouble?' ($P = 0.65$) and 'Would you recommend treatment to a friend/family member with the same condition?' ($P = 0.67$).

Four patients commented on their difficulty in smiling after a set of injections, with an onset during the first week after injections. All experienced a unilateral presentation with an inability to activate the zygomaticus major muscle, resulting in an asymmetrical smile. Three of those patients received BTX-A and one received placebo. Ten of 15 patients reported increase pain after administration of the first set of injections, with comments ranging from tenderness for 2 days to pain for 8 + weeks. On the second set of injections, four of ten patients reported an increase in pain.

4. Discussion

The high rate of dropout suggests that treatment was too painful, the side effects were unacceptable, perceived benefit too small, and/or the trial was too long and tedious to continue with. Of the five patients who dropped out, three were from the BTX-A group and two from the placebo group. It can be assumed that patients who experienced a change in facial expression thought they had received BTX-A, and therefore may not have wanted to receive the 12 placebo injections due to the production of post-injection pain. There has been published data showing that local anesthetic can be used as a vehicle for BTX-A without altering

Table 2
Characteristics of patient who dropped out of the study

Patient (treatment order)	Age (years old)	Educatioun (highest attained)	Employment (yes/no)	Litigation (yes/no)	Pain intensity VAS (mm)	Pain unpleasantness VAS (mm)	Pain duration (months)	Maximum opening without pain (mm)	Maximum opening irrespective of pain (mm)	Tender (# of points out of 12)	Reason
Patient 2 (B-P)	20	High school	Yes	No	56	30	48	39	50	10	Paralysis
Patient 6 (P-B)	38	Diploma	Yes	No	73	74	246	13	30	9	↑ Pain
Patient 8 (B-P)	43	Degree	Yes	No	56	72	216	12	49	4	Paralysis
Patient 14 (P-B)	41	High school	Yes	No	55	65	24	28	56	10	↑ Pain
Pat. 15 (B-P)	28	Diploma	No	Yes	51	58	24	24	47	6	↑ Pain

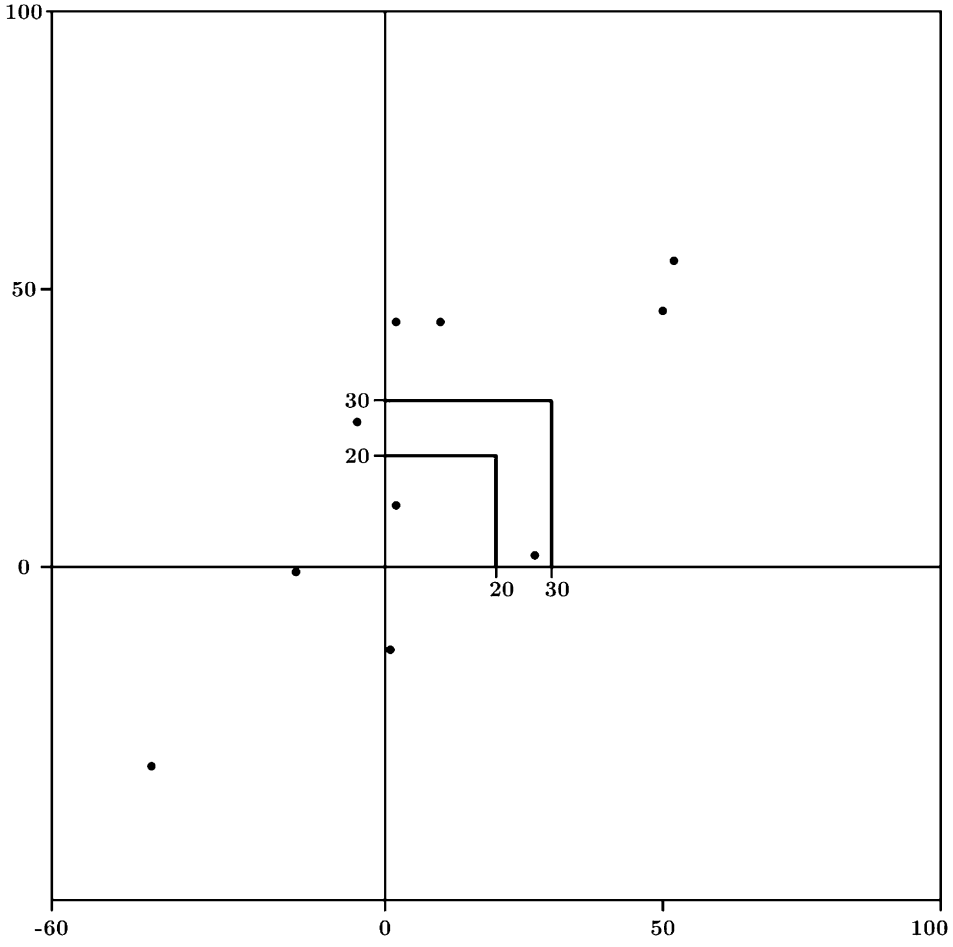

Fig. 2. VAS pain intensity and VAS pain unpleasantness differences between BTX-A and placebo groups.

the clinical effects (Gassner and Sherris, 2000). Retrospectively we would recommend the use of local anesthetic over normal saline for the administration of BTX-A.

The sporadic paralyzation of zygomaticus major was thought to be from local diffusion of the BTX-A from the masseter or direct muscle trauma from needle insertion. Electromyographic guidance was used to confirm needle tip placement within the jaw elevator muscles, so direct

Table 3
Muscle palpation tenderness expressed by muscle and by site, left and right sides of each patient combined[a]

	Baseline (%)		8 weeks (%) after BTX	Baseline (%) before placebo	8 weeks (%) after placebo	Cut-off (kg/cm^2)
	At screening	Before BTX				
Temporalis (muscles)	26/30 (87)	22/26 (85)	22/26 (85)	25/26 (96)	21/22 (95)	
Anterior (points)	20/30 (67)	20/26 (77)	15/26 (58)	21/26 (81)	20/22 (91)	1.84
Middle (points)	22/30 (73)	22/26 (85)	19/26 (73)	19/26 (73)	19/22 (86)	2.18
Posterior (points)	15/30 (50)	16/26 (62)	14/26 (54)	17/26 (65)	17/22 (77)	2.26
Masseter (muscles)	28/30 (93)	24/26 (92)	26/26 (100)	26/26 (100)	21/22 (95)	
Posterior deep (points)	25/30 (83)	20/26 (77)	24/26 (92)	25/26 (96)	19/22 (86)	1.54
Anterior superficial (points)	23/30 (77)	20/26 (77)	24/26 (92)	24/26 (92)	20/22 (91)	1.51
Inferior (points)	28/30 (93)	24/26 (92)	21/26 (81)	26/26 (100)	17/22 (77)	1.41
Total (muscles)	54/60 (90)	46/52 (88)	48/52 (92)	51/52 (98)	42/44 (95)	
Total (points)	133/180 (74)	122/156 (78)	117/156 (75)	132/156 (85)	112/132 (85)	

[a] Muscle palpation tenderness did not differ between BTX-A and placebo groups, $P = 0.91$. The difference of change (baseline values and 8 weeks) for total muscle points between BTX-A and placebo groups was used to calculate significance.

Table 4
Responses to the testable general questions, answers could be either 'yes' or 'no'

	8 week, BTX # 'yes'	8 weeks, placebo # 'yes'	*P* value
Were the injections painful?	8/10	7/10	0.64
Is treatment worth it?	8/10	8/10	0.65
Would you recommend treatment?	7/10	8/10	0.67

deposition into the muscles of facial expression is unlikely. Diffusion of BTX-A to adjacent muscles has been shown (Eleopra et al., 1996), is thought to be dose- and volume-dependent (Shaari and Sanders, 1993; Borodic et al., 1994), and increases around areas of compromised fascial integrity (Shaari et al., 1991), such as the needle puncture site. No facial muscle paralysis was reported in previous publications with injections using a smaller volume (0.1 ml) (Freund and Schwartz, 1998; Freund et al., 1999, 2000). The reasoning for using a larger volume per injection site was an attempt to reduce the number of injections while maintaining adequate diffusion throughout the muscle. Injection sites in our study also coincide with sites with published normative algometer values for palpation.

The two targets within muscle that were thought to be pertinent in this study are the motor endplate of the muscle fibers and the intrafusal muscle spindle fibers. The motor endplate band within the masseter muscle is thought to be horizontal at the middle of the lower half of the muscle, one-third the distance from the angle of the mandible to the zygomatic arch, with some individual variability (Iwasaki et al., 1990). The masseter muscle has a greater concentration of spindle fibers than limb muscles and these spindles are found in an uneven distribution throughout the muscle body, but concentrated and associated with deeper slow twitch extrafusal fibers (Rowlerson et al., 1988). Since the application of BTX-A is thought to be affected by post-injection positioning of the patient (Carruthers and Carruthers, 1997), the injection protocol in our study should have resulted in the desired paralysis effect of both intrafusal and extrafusal muscle fibers within the majority of the muscle body.

The small sample size used for this controlled study with one-third of the patients dropping out made it very difficult to draw solid conclusions on treatment effect. Post hoc power analysis revealed $1 - \beta = 0.38$ for VAS pain intensity, and $1 - \beta = 0.13$ for VAS pain unpleasantness. A difference of 20 mm on a VAS, which is thought to correlate with a two-point change on a 0–10 scale, has been determined to be a clinically significant change in pain (Farrar et al., 2001). Only two patients achieved this score in both pain intensity and pain unpleasantness scales (Fig. 2). Calculating sample size for VAS intensity, with an observed variance of 30.1 in our population, $n = 26$ for $1 - \beta = 0.90$ and a difference of 20 mm, while for VAS unpleasantness, with an observed variance of 28.7, $n = 24$ for $1 - \beta = 0.90$ and a difference of 20 mm. These results of BTX-A for myogenous orofacial pain are in stark contrast to those previously published (Freund and Schwartz, 1998; Freund et al., 1999; Freund et al., 2000). This can be explained by the fact that these reports were open-label trials, which often overestimate treatment effects (Schultz et al., 1995; Kunz and Oxman, 1998). Consistent with the results of our study is a recently published randomized controlled trial investigating neck pain where the authors reported that previous open-label trials overestimated the treatment effects of BTX-A for muscular pain (Wheeler et al., 2001).

This study did not test for dose effect and therefore patients may have been under dosed, with no to minimal muscular effect, or over dosed, with less effect (Silberstein et al., 2000). One report does outline two different doses used into the masseter muscles (Freund and Schwartz, 1998) and reduction of muscle function has been shown in follow-up trials (Freund et al., 1999, 2000). Therefore inappropriate dosing is unlikely to be the major reason for our results.

Several problems are inherent with our measure of pain. Patients may have had difficulty comprehending the difference between pain intensity and pain unpleasantness and therefore some patients may have scored them differently than others. Also, only a single point measurement in time, which was based on patient recall, was taken to represent their pain. Single measurements and patient recollection has been shown to vary considerably and hence is not the most reliable or accurate method of evaluation (Jensen, 1997).

Recent research into the possible anti-nociceptive activities of BTX-A has been published. Purkiss et al. (2000) presented data that BTX-A partially antagonizes the release of substance P when cultured dorsal root ganglion neurons are exposed to capsaicin. Ishikawa et al. (2000) reported both an anti-cholinergic and anti-substance P effect, but not anti-adrengeric, of BTX-A on rabbit iris sphincter and dilator muscles. Furthermore, Humm et al. (2000) found an increase in bilateral enkephalin expression in the rat spinal motoneurons after unilateral limb injection. While this research is interesting and promises to reveal a more complex central activity of BTX-A, our study and another well-controlled clinical trial (Wheeler et al., 2001) have failed to demonstrate a clear therapeutic advantage. The lack of clinical efficacy may be due to the utilization of small sample sizes, possible heterogeneous patient groups, inappropriate dosing regimes, or insensitive outcome measurements, but reasonable steps have been taken to minimize these potential sources of error. When new information regarding the etiology of muscular pain syndromes comes to light, as it undoubtedly will, the role of drugs like BTX-A will become more clear.

What can be concluded from our study is that patients receiving BTX-A have a relative decreased maximum opening compared to patients who received placebo. This cannot be explained by the fact that BTX-A affects the intrafusal gamma-efferent motor fibers within the muscle spindles as

well as the alpha-afferent motor fibers of the extrafusal muscle (Filippi et al., 1993; Rosales et al., 1996), since a reflective increase in maximum opening would be expected based on research on upper limb dystonias (Priori et al., 1995). This activity was initially thought to be a potential therapeutic benefit, resulting in a reflexive reduction in extrafusal muscle activity and in the 'reorganization' of central mechanism or in the change of the 'alpha-gamma linkage' (Giladi, 1997; Göbel et al., 2001; Rosales et al., 1996). The lack of both intrafusal and extrafusal muscle fiber activities may result in reduced proprioceptive feedback of muscle length and activity and with the lack of quantitative monitoring of jaw opening, self-correction would not occur. Besides visual feedback, the two papers (Giladi, 1997; Rosales et al., 1996) differ by the involved neuroanatomical structures, spinal verses brainstem, and patient populations, upper limb dystonia vs. chronic muscular pain, and these differences may be significant (Priori et al., 1995).

Evidence exists to support the concept that various central mechanisms, some unknown and some partially elucidated, are responsible for the activity of BTX-A that cannot solely be explained by extrafusal muscle paralyzation (Giladi, 1997; Göbel et al., 2001). It is conceivable that a yet undetermined mechanism is occurring. At the 8-week evaluation time alpha-gamma linkage may be enhanced particularly in the slow extrafusal muscle fibers, as a rebound effect after initial paralyzation. These fibers control resting tone of the jaw elevator muscles and modulate posture of the mandible (Goodwin and Luschei, 1975), thus explaining the decrease in opening. Further investigation is required to evaluate this hypothesis.

The cost of treatment is high and would be a huge barrier in opting for treatment for most people. The tangible costs are for the drug, approximately CDN $474 for a 100 U vial of BTX-A. Adding in a professional fee, roughly CDN $200 for administration and follow-up, and the monetary cost is CDN $1148.00 for therapy that may last up to 4 months. The intangible costs include the pain of injections, increase in orofacial pain that lasts for at least 2 days, risk of facial asymmetry due to facial muscle paralysis, and decreased ability to chew. These are obviously high enough without the monetary price to cause a dropout of one-third of the participants. With this being the case and the lack of positive treatment response, we chose not to continue with more patient recruitment to achieve greater power.

In conclusion, BTX-A was found to be costly and not effective as a treatment modality for myogenous orofacial pain in this study of female patients who reported chronic moderate to severe pain of the muscles of mastication of unknown etiology.

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