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# Localized myofascial pain responds better than referring myofascial pain to botulinum toxin injections

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*Abstract.* Myofascial pain of the muscles of mastication is a common temporomandibular disorder. Patients unresponsive to conservative treatment modalities pose a therapeutic challenge to the treating clinician. The efficacy of intramuscular botulinum toxin injections for recalcitrant cases is still not well established due to mixed results from clinical trials. The Diagnostic Criteria of Temporomandibular Disorders (DC/TMD) classified chronic muscle pain broadly into a localized pattern (when pain is localized to the site of palpation or the muscle palpated) and a referring pattern (when the pain spreads beyond the boundary of the muscle being palpated). The medical records of 25 consecutive patients treated with botulinum were analysed retrospectively. Significant pain reduction was achieved in 69.2% of the patients with localized myofascial pain and 16.7% of the patients with referring myofascial pain ($P = 0.015$). Seventy-seven per cent of the patients with localized myofascial pain reported using less analgesic throughout the follow-up period, whereas only 25% of the patients with referring myofascial pain ($P = 0.017$). The effects of botulinum toxin in responsive patients subsided after a mean of 3.21 months. Patients with localized myofascial pain benefited from botulinum toxin injections, but patients with referring myofascial pain responded poorly to this treatment.

Key words: temporomandibular disorder; myofascial pain; pain referral; botulinum toxin; myalgia.

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Myofascial pain of the muscles of mastication is a common temporomandibular disorder, and its primary feature is myogenous pain, and, to a lesser degree, mandibular dysfunction and limited range of motion[1]. The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD)[2] developed by the International Association for the Study of Pain (IASP) and the International Association of Dental Research (IADR) classified chronic muscle pain broadly into a localized pattern and a referring pattern. In localized myofascial pain, the pain is either localized to the site of palpation or spreads beyond the site of palpation but within the boundary of the muscle. In referring myofascial pain, the patient reports pain spreading to sites beyond the boundary of the muscle being palpated.

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Various therapies are available for treating chronic muscle pain, and no specific therapy has been proved to be uniformly effective. The primary mode of action of conservative therapies lies in reducing the tonicity of muscles and relaxing them, and approximately 80% of patients will gain satisfactory pain relief after undergoing one or more conservative treatment modalities[3]. Botulinum toxin (BTX) was introduced into medicine more than 30 years ago for the treatment of diseases with increased muscle tone and became the first bacterial toxin used as a medicine[3,4]. It causes temporary dose-dependent denervation of skeletal muscle by blocking the release of acetylcholine from nerve endings at the neuromuscular junction, inhibiting muscular contraction. The result is relaxation of the muscle.

Just as several studies showed statistically significant pain relief from BTX injections,[3,5–13] others showed no pain relief compared to placebo saline injections[9,14–22]. Despite numerous clinical trials, the efficacy of BTX in alleviating myofascial pain is still not well established[23]. One of the main reasons for the discrepancy found in the literature in our opinion could be differences in the diagnostic criteria and inclusion criteria used in the different trials. Various diagnostic criteria exist for myofascial pain[24]. Some studies applied inclusion criteria that would have led to the exclusion of their patients from other studies. This may cause the true effect size to be underestimated because of the inclusion of patients who are unlikely to respond to therapy, and could lead to the appearance of a negative trial, when in fact a subgroup may have experienced a genuine benefit[9]. The present study aimed to evaluate the efficacy of BTX in alleviating myofascial pain while differentiating between the two patterns of muscle pain according to the DC/TMD: localized myofascial pain and referring myofascial pain.

## Patients and methods

This was a retrospective study evaluating the outcome of the first treatment of BTX intramuscular injections in consecutive patients suffering from chronic myofascial pain treated at our department during a 2-year period (from February 2014 to March 2016). The diagnosis was based on anamnestic and clinical evaluations and patients were categorized according to the DC/TMD guidelines[2] and were divided into local myofascial pain and referring myofascial pain for analysis.

Clinically patients complained of pain in the perimandibular area that was often aggravated with jaw function, and was not associated with limited mouth opening. The pain was elicited with palpating the involved muscles, replicating the chief complaint. The diagnosis of local myofascial pain was given to patients when pain was localized to the site of palpation or the muscle palpated. Tender sites were palpated for approximately 5 seconds to ensure the pain did not refer to distant sites. A diagnosis of referring myofascial pain was given to patients experiencing pain spreading beyond the boundary of the muscle being palpated.

Patients to be treated with BTX at our department had to meet the following criteria:

- Failure to achieve satisfactory response to previous conservative therapies consisting of rest, habitual modifications, self exercises, office-based physical therapy program, pharmacologic treatment (a benzodiazepine with or without a non-steroidal anti-inflammatory drug), and either a 3-month period of occlusal splint therapy or a 3-month trial with Tricyclic antidepressants.
- Constant pattern of pain localization and characteristics in at least two different clinical examinations. Undefined pain patterns with poor localization were not candidates for BTX injections.
- Absence of concomitant intra-articular temporomandibular joint disorders.

All conservative therapies were discontinued when the decision to undergo BTX injections was made, which was usually several weeks before the injection appointment. Botox (Allergan pharmaceuticals, Mayo, Ireland), which is a type-A BTX was used in all cases. An ampoule of 100 MU was diluted in 1 mL of normal saline. The injections were given on an individual basis into points of tenderness in painful muscles, and were individualized to each patient depending on the pain location and laterality. Only painful muscles were injected, and as close as possible to the tender points. Patients first identified the areas of pain by pointing with their fingers or hands; then the examiner palpated the tender spot and the surrounding areas, checking for additional tender points and possible referral points. The involved muscle was palpated during clenching and relaxation. BTX was injected directly into or as close as possible to the clinically identifiable tender points in the affected muscles, with two to four injections per tender muscle. In cases of myofascial pain with referral, no attempt was made to inject the distant sites to which the pain referred to, rather the injections were given to the muscle being palpated. The most common areas to which the pain referred to were the eyebrow, forehead, vertex, and occiput. All injections were performed by one surgeon (W.A.) and immediately after dilution of the toxin. Each injection point received 0.1 mL of solution containing 10 MU of BTX. A 23G 30-mm-long needle was used to inject the masseter, anterior portion of temporalis, sternocleidomastoid, and posterior digastric muscles. A 27G 15-mm-long needle was used to inject the middle and posterior areas of the temporalis muscle. A 27G 37-mm audio-amplified electromyographic (EMG) needle was used to inject the medial pterygoid muscle. The antero-inferior portion of the temporalis muscle was injected in two different depths: a superficial injection at the depth of the medial surface of the zygomatic arch, and a deep injection when the needle contacted bone at the outer surface of the lateral orbital wall (Fig. 1). All injections were performed transcutaneously. Patients were asked to clench their teeth and open wide every 10 minutes in the few hours

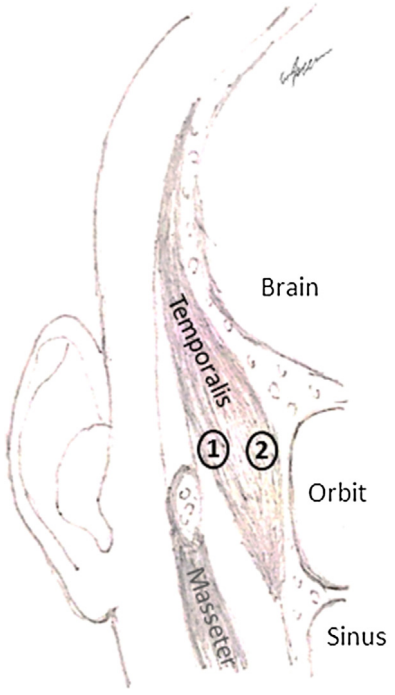


*Fig. 1.* Coronal section illustrating the two different depths of injection into the antero-inferior portion of the temporalis muscle: 1, superficial injection point at the depth of the medial surface of the zygomatic arch; 2, deep injection point when the needle contacts bone at the outer surface of the lateral orbital wall.

following the injections, as muscular activity facilitates more efficient incorporation of toxin into the endplates. Patients were allowed to use analgesics as required in the postoperative period. Muscle relaxants were not prescribed, and none of the patients underwent office-based physical therapy programme in the following months.

Pain evaluations were conducted at each follow-up examination and documented in the medical records as a routine practice and not for the conduction of a clinical trial. For the purpose of this study the data was drawn from the medical records retrospectively and analysed. At each follow-up examination, patients were asked to evaluate the level of pain compared with pre-treatment on a four-level scale. The patients were asked whether there was a ''Significant improvement'' in pain levels, ''Moderate improvement'' in pain levels, ''No improvement'', or ''Worse'' pain compared with baseline. The follow-up assessments conducted at 1 month, 2 months, and approximately 4 months postoperatively were used to evaluate response to treatment. This was considered the primary outcome variable. The secondary outcome variables were request to undergo additional BTX treatment after the effect has waned, and use of analgesics throughout the follow-up period.

### Statistical analysis

Comparison of continuous parameters was performed using the *t*-test. Comparison of categorical variables was performed by the Fisher exact test. In all analyses a $P < 0.05$ was considered significant. The statistical software program used was SPSS ver.23.0.

The study was approved by the institutional ethical review board, which waived informed consent. The study conformed to guidelines of the Declaration of Helsinki.

## Results

Twenty-five patients underwent BTX injections for the first time and attended at least two follow-up examinations at 1 and 2 months postoperatively and were included in the study. The mean age was 46.5 years (range 20–71), and 68% of the patients were female. Thirteen patients were diagnosed preoperatively as suffering from localized myofascial pain and 12 patients from myofascial pain with referral. The duration of pain ranged from 1.5 to 6 years, with an average of 4.1 years. There was no significant difference between the two groups with regard to age, gender, and duration of disease (Table 1).

*Table 1*. Descriptive characteristics of the study population.

| |
|---|
| Gender |
| F: 17 patients (68%) |
| M: 8 patients (32%) |
| Diagnosis |
| Localized myofascial pain: 13 patients (52%) |
| Referring myofascial pain: 12 patients (48%) |
| Age |
| Average: 46.5 years |
| Range: 20 to 71 years |
| Duration of symptoms |
| Average: 4.1 years |
| Range: 1.5 to 6 years |
| Laterality |
| Bilateral: 15 patients (60%) |
| Unilateral: 10 patients (40%) (L:R 7:3) |
| Number of muscles injected (per patient) |
| Average: 3.1 muscles per patient |
| Range: 1 to 6 muscles per patient |
| Dose of BTX injected (per patient) |
| Average: 83.2 MU per patient |
| Range: 30 to 180 MU per patient |

Patients received amounts ranging from 30 to 180 MU of BTX, injected into one to six muscles, uni- or bilaterally. The decision on the location and number of injection points depended on the pattern of each patient's individual complaint. Fifteen of the 25 patients (60%) had bilateral complaints and received bilateral injections (Table 1). The most commonly injected muscle was the masseter (injected in 22 patients, 88%), followed by the temporalis (19 patients, 76%), sternocleidomastoid (7 patients, 28%), posterior digastric (2 patients, 8%), and medial pterygoid (2 patients, 8%).

The primary outcome variable was the patients' self-reported evaluation of pain reduction after treatment. At the 1-month follow-up evaluation, eight of the 13 patients (61.5%) with localized myofascial pain and four of the 12 patients (33.3%) with referring myofascial pain reported ''Significant improvement'' in pain levels. The difference was not statistically significant ($P = 0.237$). At the 2-month follow-up examinations, nine patients (69.2%) with localized myofascial pain achieved ''Significant improvement'' whereas the proportion of ''Significant improvement'' in the referring myofascial pain group dropped to two (16.7%). This difference was statistically significant ($P = 0.015$) (Table 2). None of the patients reported worsening of symptoms after treatment. Many patients did not attend a third follow-up visit at approximately 4 months after the injections. Evaluations of only 10 of the 13 patients with localized myofascial pain and six of the 12 patients with referring myofascial pain were available; therefore as much as 36% of the study population was lost to follow-up at this time point. Of interest, all the patients previously achieving ''Significant improvement'' attended the 4-month follow-up examinations, whereas only few of those reporting ''Moderate improvement'' and ''No improvement'' did. A clear trend towards deterioration into baseline pain values was evident for both groups; six of the nine patients with localized myofascial pain previously reporting ''Significant improvement'' regressed to baseline pain values and reported the effects of the injections have waned, and similarly the two patients with referring myofascial pain previously reporting ''Significant improvement'' both reported to regress to baseline values at the 4-month evaluation. The average duration of BTX effects on pain was 3.21 months, with no significant difference between the two groups. Many patients reported waning of the analgesic effect over a few days.

The two secondary outcome variables were use of analgesic drugs and patient's request for additional BTX injections (Table 3). Patients were asked about use of analgesics at each visit, and if used the frequency, type, and dose. The majority of

*Table 2*. Primary outcome variable: improvement in pain.

| | 1 month | | | 2 months | | | ~4 months | | |
|---|---|---|---|---|---|---|---|---|---|
| | LMP | RMP | *P* | LMP | RMP | *P* | LMP | RMP | *P* |
| Significant improvement | 8/13 (61.5%) | 4/12 (33.3%) | 0.237 | 9/13 (69.2%) | 2/12 (16.7%) | 0.015 | 3/10 (30%) | 0/6(0%) | 0.25 |
| Moderate improvement *and* no improvement | 5/13 (38.5%) | 8/12 (66.7%) | | 4/13 (30.8%) | 10/12 (83.3%) | | 7/10 (70%) | 6/6 (100%) | |
| Total | 13 (100%) | 12 (100%) | | 13 (100%) | 12 (100%) | | 10 (100%) | 6 (100%) | |

LMP, localized myofascial pain; RMP, referring myofascial pain.

*Table 3*. Secondary outcome variables: using less analgesic and request for additional BTX injections.

| | Using less analgesic | | | Request for additional BTX | | |
|---|---|---|---|---|---|---|
| | LMP | RMP | *P* | LMP | RMP | *P* |
| Yes | 10/13 (77%) | 3/12 (25%) | 0.017 | 7/10 (70%) | 3/6 (50%) | 0.51 |
| No | 3/13 (23%) | 9/12 (75%) | | 3/10 (30%) | 3/6 (50%) | |
| Total | 13 (100%) | 12 (100%) | | 10 (100%) | 6 (100%) | |

LMP, localized myofascial pain; RMP, referring myofascial pain.

patients with localized myofascial pain (10 of 13) reported using less analgesic throughout the follow-up period, whereas only three of the 12 with referring myofascial pain reported so ($P = 0.017$). At the 4-month visit, patients were asked about their willingness to undergo a second BTX treatment. Of the 10 patients with localized myofascial pain who continued to be followed up at this time, seven requested additional BTX treatment after reporting the effects of the injections had subsided. Of the six patients with referring myofascial pain attending the 4-month visit, three expressed willingness to undergo additional BTX treatment ($P = 0.51$).

The total dose of BTX injected per patient was considered the predictor variable. Patients received amounts ranging from 30 to 180 MU, injected in one to six muscles, uni- or bilaterally. The average amount of BTX injected for the study cohort was 83.2 MU per patient. Those achieving ''Significant improvement'' received a mean of 85.4 MU in 3.3 muscles on average, while those reporting ''Moderate improvement'' and ''No improvement'' after treatment received on average 81.4 MU in 2.9 muscles. The difference was not statistically significant ($P = 0.792$ and 0.453, respectively).

The treatment was well tolerated. Post-injection tenderness was infrequent and mild and consisted of 1 or more days of localized discomfort. Two patients that received injections into the masseter muscles complained of an asymmetric smile that probably resulted from weakening of the zygomaticus muscles on the injected side. The paresis resolved after approximately 3 months.

## Discussion

BTX administered intramuscularly to alleviate chronic myofascial pain produced significant temporary analgesia in patients with localized myofascial pain but failed to achieve similar results in referring myofascial pain, when the pattern of pain included referral to distant sites.

The onset of pain reduction was relatively delayed, probably because the analgesic effect of BTX-induced muscle relaxation builds up gradually, reaching a peak after more than a month of continued muscle relief. Similar to the more common conservative treatment modalities aiming to relax muscles, the analgesic effect appears after a period of continued and sustained relaxation of the painful muscle fibres. The effect of BTX lasts a little more than 3 months. In the present study, more than half the patients reported returning to pre-injection pain levels approximately 3 months after the injections. In view of the consistency between the period without pain and the termination of the toxin's clinical effect, it may be stated that the source of the effect was the toxin[15].

The majority of conservative treatments for myofascial pain aim to achieve, among other goals, muscle relaxation[25,26]. The primary goal of occlusal splints, physiotherapy, behavioural interventions, and rest is in the reduction of muscle tonicity. Pharmacologic muscle relaxants, anxiolytics, hypnotics, and antidepressants achieve, among other effects, muscle relaxation to a great extent[27]. BTX has been successfully used for diseases with increased muscle tone for about 30 years[3]. Strabismus, blepharospasm, facial wrinkles, spasticity, muscular hypertrophy, cervical and oromandibular dystonia, and various movement disorders are treated effectively with BTX intramuscular injections. The toxin causes temporary dose-dependent denervation of skeletal muscle, attenuating muscular contraction. Reports on its efficacy in improving myofascial pain began to emerge in the 1990s[20,28]. Nowadays, many experienced and skilled clinicians use BTX effectively in their daily practice for the treatment of myofascial pain[23].

Several mechanisms have been suggested to explain the pathophysiology behind myofascial pain syndrome, such as motor end plate hyperactivity, ischaemic muscle spasm, neuromuscular dysfunction, and central sensitization. Some of these models complement each other, and the syndrome is very likely to be a consequence of more than one of these purported mechanisms[29]. Most hypotheses agree that abnormal patterns of muscle contraction are, in large part, responsible for maintaining muscle pain[29–33]. An initial injury in the form of repetitive parafunction, chronic malpositioning, etc., can cause stimulation of nociceptors, which may lead to tonic excitation of motor neurons. This muscular hyperactivity leads to spasm, which leads to further stimulation of nociceptors. This vicious cycle of sensitized nociceptors and focally hyperactive motor neurons is probably the basis of myofascial pain[26,31]. Needle electromyography (EMG)-based studies have reported that sustained spontaneous EMG activity can be found within 1–2 mm of the hyperirritable or tender point in a muscle, but not from non-painful control sites[26,34]. The spontaneous activity recorded from the trigger points is probably related to excessive release of acetylcholine at the neuromuscular junction[5,26]. When injected into points of tenderness, BTX reduces the excess acetylcholine leaking from the hyperirritable and dysfunctional endplates, causing muscle relaxation and reducing pain. Muscle relaxation in turn has many other virtues. It releases compressed neighbouring capillaries improving blood flow, improves aerobic muscular metabolism with regard to oxygen supply by reducing local hypoxemia, releases adjacent sensory nerve fibres decreasing their release of neurovasoactive substances and neurotransmitters, and decreases inflammatory processes within the muscle[3,5,8,14,17,23,24].

There is great discrepancy in the literature regarding the efficacy of BTX injections for treating myofascial pain[3,5–13]. In our opinion, different diagnostic criteria and inclusion criteria used in the different studies could be one of the main reasons for this discrepancy. Various diagnostic criteria exist for myofascial pain[24]. Some studies applied inclusion criteria that would have led to the exclusion of their patients from other studies. This may cause the true effect size to be underestimated because of the inclusion of patients who are unlikely to respond to therapy, and could lead to the appearance of a negative trial, when in fact a subgroup may have experienced a genuine benefit[9]. In the present study, had the patients been included in one heterogeneous group, and not divided into two distinct groups, the outcomes would have been much less conclusive. In their systematic review of the literature, Chen et al.[35] recommended evaluating the efficacy of BTX injections for the different types of chronic muscle pain separately to

evaluate the actual therapeutic efficacy of BTX on pain.

Another reason for the discrepancy between trials could be differences in the number and location of injection points, and the total dose injected. This correlates directly with the location and extent of denervation and, consequently, improvement in pain[9,10]. Some studies performed standardized bilateral injections even for patients with unilateral complaints[15]. Others gave fixed dose portions of BTX for the masseter and temporalis, regardless whether only one or both muscles were painful[15,18,20].

Other issues that may contribute to the mixed results found in the literature could be differences in postoperative therapy, flaws in solution preparation and injection technique, unsuitable storage of solution, different methodologies used to assess outcomes, short span of follow-up period, different chemical makeup of BTX preparations, and differences in response to BTX between individuals. All these factors contribute to the large discrepancy found between trials and hamper comparability among them.

Opponents for the use of BTX to treat myofascial pain argue that hyperactivity as an etiologic factor has not been proven, and the hyperactivity recorded by EMG from tender points is not a consistent finding. These investigators rely primarily on the pain adaptation model, which was developed after several studies found that EMG activity in painful muscles at rest was similar to normal muscles, and that during concentric contraction, EMG activity or force output was actually lower in painful muscles than in normal controls[30]. On this basis, producing paresis of the involved muscles seems illogical. Indeed pain inhibits motoneuronal output to contracting muscles, but this is probably adaptive to help prevent further damage and promote healing. In addition, the disuse of muscles in chronic pain undoubtedly causes some degree of atrophy. The previously mentioned studies were conducted by eliciting pain to a muscle by various methods, and then performing EMG activity of the muscle to find no evidence of increased hyperactivity[30,36]. In our opinion, the fact that pain causes the muscle to become hypoactive does not mean that further reducing the activity of the painful muscle does not improve pain.

There are only few well-designed prospective randomized controlled trials (RCTs) comparing BTX injections to saline injections. Some of these articles concluded that the efficacy of BTX injections is merely the result of the needling per se. Nixdorf et al.[20] in a prospective double-blind crossover RCT examined 15 patients and found the mean pain reduction on a visual analogue scale (VAS) to be 19 mm for the BTX group and only 1 mm for the placebo group; however, the results were statistically insignificant. The authors concluded that BTX is not efficacious for treating myofascial pain; however in our opinion, the statistical insignificance could have resulted from the small cohort (15 patients) or the large drop-out rate (one-third of the subjects). Ernberg et al.[18] evaluated 21 patients in a prospective double-blind crossover RCT. The average pain scores decreased significantly more in the BTX group than in the saline group; however, the authors concluded that the efficacy of BTX was not impressive, because the number of patients who experienced significant reduction in pain (in the authors opinion at least 30%) was not significantly higher in the BTX group than in the saline group. Von Lindern et al.[3], on the other hand, evaluated 90 patients and found the opposite. They conducted a prospective blinded RCT and found a reduction in pain levels in 91% of the patients receiving BTX injections, a significantly higher proportion than the patients receiving saline. Sidebottom et al.[5] prospectively evaluated 62 patients receiving BTX injections for myofascial pain. The evaluations were performed 6 weeks after the injections and revealed that 79% of the subjects reported pain reduction, and 56% reported pain levels reduced to minimal. Guarda-Nardini et al.[37] published a double-blind RCT with a 6-month follow-up. Twenty patients with bruxism and myofascial pain were evaluated. Improvements in the BTX group were higher than in the saline group; however, in some outcome measures there was no statistical significance. The authors concluded that a larger cohort could have resulted in statistical significance for all outcome variables and that BTX is an efficacious treatment modality for chronic myalgia.

Pain assessments are inherently subjective, and there are many methods proposed to assess pain changes, the variability of which emphasizes that no single method is superior to others. The VAS is recommended to assess changes in pain levels primarily because it is an easily administered, widely popular, and a relatively reliable tool. It has some drawbacks, though, such as difficulty for patients to comprehend the scale, and the lack of verbal anchors that may create ambiguity, which could affect a patient's responsiveness and compliance with it. The present study utilized three different scales to assess improvements in pain levels and overall satisfaction (four-level verbal evaluation, use of analgesics, and request for a second BTX treatment). It is well accepted that multiple outcome measures reduce the risk of bias in the evaluation of subjective outcomes[38–40].

Recent studies have shown that BTX type-A reaches the brain and spinal cord 48 hours after intramuscular injection. It was hypothesized that it may have a direct analgesic effect on the sensory nociceptive systems that go far beyond the peripheral denervation in the neuromuscular junction3. Animal studies have shown that subcutaneous injections of BTX inhibit the release of substance P, glutamate, bradykinin, and calcitonin gene-related peptide, thus proposing a direct inhibitory effect on the central nervous system (CNS) and the spinal cord[9,18,23,24,29]. Whether this has any clinical relevance remains to be seen. The present study found BTX to be ineffective for treating patients with pain referral. There is a consensus that mechanisms of the peripheral and central nervous systems can cause the pain in temporomandibular disorders. Patients with referred pain probably have more central neuronal changes in their pain system[26,41]. Our results raise the possibility that BTX is probably less effective in cases of enhanced CNS processing of painful stimuli that is characteristic of central sensitization.

Despite current treatments with physical therapy, pharmacologic therapy, behavioural modifications, and occlusal treatments, myofascial pain remains a challenging condition in clinical practice. The results of this study add to the body of evidence for beneficial effects of BTX in cases recalcitrant to conservative measures. Localized myofascial pain was found responsive to the toxin, with 69.2% of the patients reporting significant improvement 2 months after the injections. Patients with referring myofascial pain failed to achieve similar results. Future studies should utilize questionnaires addressing changes in quality of life and dysfunctional activities after treatment, in addition to the assessment of pain. Future prospective controlled trials with large cohorts and strict diagnostic criteria are required to further investigate BTX with regard to efficacy for the different types of myofascial pain, cumulative effects of repeated injections, and recommended post-injection therapeutic regimens.

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None.


## Competing interests

None.

## Ethical approval

The study was approved by the institutional ethical review board which waived informed consent. The study conformed to guidelines of the Declaration of Helsinki.

## Patient consent

Not required.

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