



# Efficacy of botulinum toxin type A for treatment of persistent myofascial TMD pain: a randomized, controlled, double-blind multicenter study

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## ABSTRACT

Evidence of an effect by botulinum toxins is still lacking for most pain conditions. In the present randomized, placebo-controlled, crossover multicenter study, the efficacy of botulinum toxin type A (BTX-A) was investigated in patients with persistent myofascial temporomandibular disorders (TMD). Twenty-one patients with myofascial TMD without adequate pain relief after conventional treatment participated. A total of 50 U of BTX-A or isotonic saline (control) was randomly injected into 3 standardized sites of the painful masseter muscles. Follow-up was performed after 1 and 3 months, followed by a 1-month washout period, after which crossover occurred. Pain intensity at rest was the primary outcome measure, while physical and emotional function, global improvement, side effects, and clinical measures were additional outcome measures. There was no main difference between drugs (ANOVA;  $P = .163$ ), but there was a significant time effect ( $P < .001$ ), so BTX-A reduced mean (SD) percent change of pain intensity by 30 (33%) after 1 month and by 23 (30%) after 3 months compared to 11 (40%) and 4 (33%) for saline. The number of patients who received a 30% pain reduction was not significantly larger for BTX-A than after saline at any follow-up visit. The number needed to treat was 11 after 1 month and 7 after 3 months. There were no significant changes after treatment in any other outcome measures, with the exception of pain on palpation, which decreased 3 months after saline injection ( $P < .05$ ). These results do not indicate a clinical relevant effect of BTX-A in patients with persistent myofascial TMD pain.

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## 1. Introduction

Temporomandibular disorders (TMD) comprise a group of chronic pain conditions affecting the temporomandibular joint and masticatory muscles. The most common symptom is myofascial pain from masticatory muscles, which is often poorly localized and commonly referred to the neck, face, teeth, or preauricular regions. It is frequently accompanied by headache and restricted jaw opening capacity [49]. The prevalence of TMD is reported to be 5–10%, with a higher prevalence among women than men [5,22,28].

The pathogenesis of myofascial TMD is unclear, but psychological factors and tooth grinding/clenching are often mentioned as important etiologic risk factors [21,29,57]. Because of lack of knowledge about underlying mechanisms, a multimodal approach with reversible (conservative) treatment is usually recommended, including counselling, physiotherapy, and occlusal splints. This

treatment regime is often efficacious, but for some patients, pain does not resolve [27].

Intramuscular injections with botulinum toxin (BTX) are used in the treatment of movement disorders associated with, eg, increased muscle tone such as spasticity and dystonia, and autonomic disorders associated with cholinergic overactivity, eg, hyperhidrosis [35]. BTX causes muscle relaxation by temporarily blocking the release of acetylcholine from presynaptic cholinergic nerve terminals. The muscle remains paralyzed until new synaptic connections form as a result of sprouting [48]. With time, sprouting is reversed and the original nerve terminal is restored [6,34]. BTX is also reported to have an antinociceptive effect by blocking the release of inflammatory mediators, such as substance P and glutamate [1,41]. Because of its muscle-relaxing and possible analgesic effects, BTX has also gained much interest as a possible treatment of myofascial pain and headache disorders [7]. However, 4 recent systematic reviews, including 1 Cochrane review and 1 meta-analysis, do not support the use of BTX for myofascial neck pain or tension-type headache [20,38,42,63], although there seems

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to be some evidence for its efficacy in few other musculoskeletal conditions [35,63]. The results of the few randomized and placebo-controlled trials (RCT) in myofascial TMD are also conflicting. Two RCTs, 1 single-blind study [59], and 1 double-blind study [19] reported a better effect of BTX in orofacial muscle pain due to muscular hyperactivity. In contrast, 2 other double-blind RCTs reported no significant effect of BTX in patients with chronic orofacial pain of masticatory muscles [36] or myofascial TMD pain [25]. Finally, a study in patients with sleep bruxism reported decreased muscle activity in the masseter muscle after BTX but did not assess pain variables [26]. Different patient samples, methodologies, and sample sizes may explain these differences.

From a clinical viewpoint, BTX, if shown to be efficacious, might be used to manage myofascial TMD pain. On the other hand, as a result of the high cost of the drug in comparison to other treatments, it would probably not be the first choice. But in those patients where pain does not resolve after conservative treatment, BTX might be used as an adjunct. The aim of this study was therefore to test the hypothesis that BTX type A (BTX-A) is more effective than isotonic saline for the treatment of persistent myofascial TMD pain.

## 2. Materials and methods

### 2.1. Patients

Twenty-one patients with TMD of muscular origin were recruited between September 2004 and December 2009. The patients were recruited from patients who were either treated at the orofacial pain clinics at Karolinska Institutet, Eastman Institute, Malmö University, or Aarhus University, or were referred to these clinics because of persistent myofascial TMD pain.

Inclusion criteria were age >18 years, a diagnosis of myofascial pain according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) [12] with pain that persisted in spite of conservative treatment for at least 6 months, and an average pain intensity from the craniofacial region of  $\geq 30$  mm on a 0–100 mm visual analogue scale (VAS) during 1 week before examination. The RDC/TMD are commonly used in TMD research and have been found to provide acceptable reliability and validity [23,45]. Exclusion criteria were systemic inflammatory connective tissue diseases (eg, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), whiplash-associated disorder, fibromyalgia, neuropathic pain or neurological disorders, pain of dental origin, use of muscle relaxants, or aminoglycoside antibiotics.

The Regional Ethical Review Board in Stockholm (03/544 and 04-386T), the Regional Ethics Committee in Aarhus (2004/0010), the Medical Product Agency in Sweden (151:2003/67293), and the Danish Medicines Agency (2612-2409) approved the study. Good clinical practice guidelines were followed, and the patients received both verbal and written information about the study. Written consent was obtained for participants as well as for the processing of personal data.

### 2.2. Experimental protocol

A randomized and double-blind crossover design was used: all patients received both BTX-A and control vehicle but in different orders. Randomization was performed for all centers together by an Internet-based computer program (<http://www.randomization.com/>) in blocks of 4 patients (block size unknown to investigators) by a laboratory technician not otherwise involved in the study. For each patient, a file holder with the case report form (CRF) was made, and a note with the order of drugs for the patient

was put in a sealed opaque envelope that was attached to the CRF. The CRFs were delivered to the clinics upon request.

The patients were examined on 7 occasions. During the first visit, the patients were screened for trial suitability. If they fulfilled all inclusion criteria and none of the exclusion criteria and they agreed to participate, they were informed about the study and written approval was obtained. They were told that they would receive both BTX-A and saline but that the order of injections would be unknown to them and the investigator, and that they should continue with their usual TMD treatment to minimize the risk of confounding the results of the study. A 1-week run-in period was used for daily pain assessments before the next visit, when the patient returned to the clinic for baseline recordings and the first injection (visit 2). Follow-up occurred after 1 month (visit 3) and 3 months (visit 4). To ensure that no BTX-A effect remained, the patient did not return to the clinic for new baseline recordings and the second injection until after an additional washout period of at least 4 weeks (visit 5). Follow-up occurred as after the first injection (visits 6 and 7). Fig. 1 shows a flow chart of the study.

Before the study started, the examiners met for a training session, during which they were calibrated according to the RDC/TMD examination and they were shown the injection technique using electromyographic (EMG) guidance by a neurologist with expertise in BTX-A injections. Two patients with persistent myofascial TMD, otherwise not included in the study, were recruited for the training session.

### 2.3. Baseline recordings

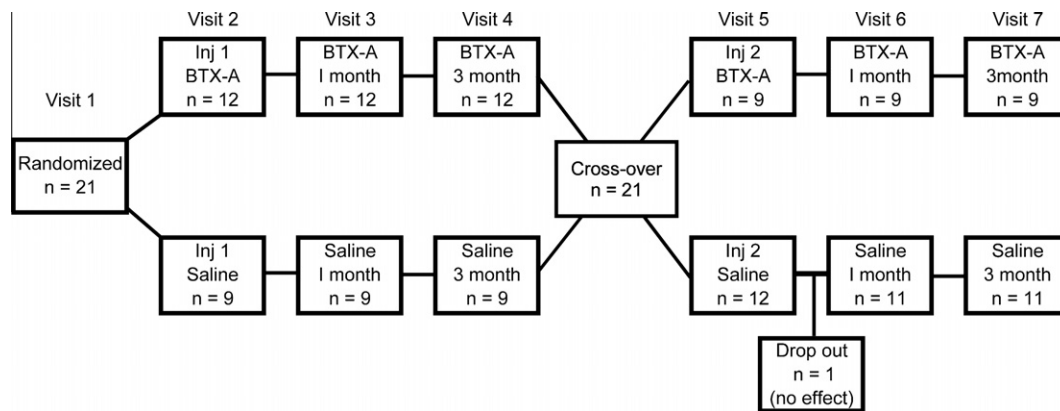
The patients were asked to mark their pain distribution on pain drawings of the head and body and to fill in the McGill Pain Questionnaire (MPQ) and the questionnaire included in axis II of the RDC/TMD [12]. They were also asked about use of analgesics, and if used, the frequency. The RDC/TMD questionnaire includes questions about pain location and frequency; general health; socioeconomic status; and awareness of temporomandibular joint sounds and tooth clenching or grinding. It also includes the Graded Chronic Pain Scale, Jaw Disability Checklist, and Symptom Checklist-90 Revised (SCL-90R).

A clinical examination comprising mandibular movement capacity, pain at movements, presence of joints sounds, and palpatory pain of the temporomandibular muscles and joints was performed in accordance with the RDC/TMD examination [12].

### 2.4. Injections

The preparation of drugs and syringes was made by a research assistant. BTX-A was prepared by dissolving 100 U of freeze-dried BTX-A (Botox; supplied by Allergan Norden AB, Upplands Väsby, Sweden) into 1.0 mL of room-temperature sterile isotonic saline. This was performed immediately before injection. A total of 1.0 mL of isotonic saline served as control. The research assistant handed over the syringe with the drug to be injected to the investigator's dental assistant to ensure that the patient, the investigator, and the dental assistant were blinded. BTX-A and saline have the same colorless appearance.

Injections were administered with EMG guidance using an audi-amplified device (Allergan Norden AB) to ensure intramuscular administration. A 1-mL syringe with a 19-mm-long needle (diameter 0.4 mm) was used for injections. The solution was injected at a depth of approximately 15 mm after careful aspiration. If aspiration indicated intravascular administration, the needle was slightly moved and aspiration repeated until negative. The solution was then delivered into 3 standardized points of each masseter muscle, such that 0.1 mL was injected into the deep (posterior) portion of the muscle, while the origin and attachment of the superficial



**Fig. 1.** Flow chart. At a screening visit (visit 1) the patients were examined for trial suitability and if included they were randomized to receive either BTX-A or control (saline). At least 1 week thereafter, the patient returned to the clinic for the first injection (visit 2) with follow-up after 1 (visit 3) and 3 months (visit 4). After at least 4 weeks, washout crossover occurred and the second injection was provided (visit 5), with follow-ups as after injection 1 (visits 6–7).

portion each received 0.2 mL [36]. Thus, the total dose of BTX-A was 50 U per muscle, ie, a maximum dose of 100 U to the patient if both muscles were treated.

## 2.5. Treatment outcome

The Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) recommends multiple outcome measures in chronic pain studies [10,11,55]. According to their recommendations, we included assessment of pain, physical function, emotional function, global improvement, and side effects as the main outcome measures. Additional outcome measures were use of analgesics, pain-free jaw opening capacity, palpatory pain of masticatory muscles (20 sites), and pressure pain threshold (PPT) and tolerance (PPTol).

### 2.5.1. Pain variables

Patients mapped pain locations outside the craniofacial region on full body pain drawings and jaw pain on facial pain drawings. During the week before the injections and follow-up visits, patients assessed their pain intensity in the craniofacial region twice daily (morning and evening) on a 100-mm VAS with the endpoints “no pain” and “worst imaginable pain.” From these data, the least, average, and maximum pain intensity during the 7 days was drawn. Changes (%) in average weekly pain score after treatment served as the primary outcome measure. A 30% reduction in pain intensity has been shown to be equivalent to “much improved” on the Patient’s Global Impression of Change Scale (PGIC), and a 50% reduction to “very much improved” [15]. A 30% reduction is considered clinically significant [14] and is recommended by IMMPACT [10]. The number needed to treat—that is, the number of patients who needs to be treated for one to have a positive outcome—was calculated on an intent-to-treat basis using the numbers of patients with 30% and 50% pain reduction.

The Graded Chronic Pain Scale was used to calculate the Characteristic Pain Intensity (CPI), which is the mean value of the current pain intensity and the average as well as the worst pain intensity during the previous 6 months. The CPI has been reported to have acceptable reliability [53].

### 2.5.2. Physical functioning

The influence of pain on daily activities was assessed with the Graded Chronic Pain Scale by calculating the disability points (DPs). This is a score composed of the number of days that the patient refrained from her or his usual activities (work, school, or

housework) because of facial pain and the mean value of the interference (assessed with a 0–10 numerical rating scale) on work capacity and on daily and social activities. The score ranges from 0 to 6, and higher scores indicate higher disability. The DPs and CPI are then combined to form 4 classes: grade I, low disability and low pain; grade II, low disability and high pain; grade III, moderate pain-related disability; and grade IV, severe pain-related disability [37]. The scale is reported to have acceptable to excellent reliability, validity, and clinical utility [13,37].

### 2.5.3. Emotional functioning

The degrees of depression and nonspecific physical symptoms (somatization) were assessed with the SCL-90R. This is an instrument used as a screening tool for psychological distress and consists of 32 questions, 20 for depression and 12 for somatization. Each question has 5 alternatives (0 = not at all, 1 = a little bit, 2 = moderately, 3 = quite a bit, 4 = extremely). The total score for the scales is calculated and divided by the number of responses, so both scores range 0–4. The scale is reported to have acceptable reliability and validity [13,37].

### 2.5.4. Global improvement

The patient’s global assessment of treatment outcome was made using the Pain Relief Scale [14] and a 7-point PGIC scale with these alternatives: symptom-free, much improved, improved, no change, worse, much worse, and very much worse [14]. This is the scale recommended by IMMPACT as a core outcome measurement for global assessment of treatment outcome [10]. IMMPACT also recommends that the percentages of patients responding to each of the 7 options in each treatment group should be analyzed and reported separately.

### 2.5.5. Additional outcome measures

Use of analgesics was assessed on a 5-point point Likert scale where 0 = never, 1 = 1–2 times a month, 2 = once a week, 3 = several times every week, and 4 = daily [56]. The patients were also asked which analgesics they received and the dose.

The maximum pain-free jaw opening (mm) was measured with a ruler between the right maxillary and mandibular first incisors with addition of the vertical overbite in accordance with the RDC/TMD examination form [12].

Palpatory pain was recorded bilaterally over 8 extraoral sites (the posterior, middle, and anterior temporalis muscle; the origin, body, and insertion of the masseter muscle; the posterior mandibular region [stylomandibular/posterior digastricus region]; and the

submandibular region [medial pterygoid/suprahoid/anterior digastricus region]) and over 2 intraoral sites (the lateral pterygoid area and the tendon of the temporalis muscle). The patient rated the pain that was elicited on a 4-point scale (0 = no, 1 = mild, 2 = moderate, 3 = severe pain) [12]. The palpation count—that is, the sum of muscles that were painful upon palpation (ranging 0–20)—was used in statistical analyses.

The PPT over the superficial masseter muscle was recorded bilaterally over the relaxed masseter muscles and an extracranial control point (the soft tissue close to the base of the thumb on the dorsal side of the right hand) with an algometer (Somedic Sales AB, Höör, Sweden). The most prominent point of each masseter muscle (determined during contraction) was used. The algometer has a blunt rubber tip of 1 cm<sup>2</sup> and a pressure rate of 30 kPa/s was used. The recordings were repeated twice with a relaxation interval of 2 min. The mean value of the 3 recordings was used as baseline value. After another 2 min, the PPTol was recorded once over the same points. In the statistical analyses, the average PPT and PPTol of the right and left side was used if the patient had bilateral pain, and the PPT and PPTol of the painful side was used if the patient had unilateral pain.

#### 2.5.6. Adverse events

The patients were asked to list any adverse event, its duration (hours, days), and its severity (mild, moderate, or severe) daily during the first week after the injections. Adverse events that had occurred since the last visit were recorded in the CRF at the follow-up visits at 1 and 3 months.

#### 2.6. Statistical analysis

The sample size was based on previous work showing that a 30% pain reduction on a 0–10 numerical rating scale is clinically relevant [15]. Because the patients serve as their own control, a power calculation showed that 18 patients would be sufficient to obtain more than 90% power when  $\alpha = 0.05$ .

The Shapiro–Wilks test was used to test the normality of data. Data are presented as number of patients (frequency) as well as mean and SD or median and interquartile range (IQR), ie, the difference between the 75% and the 25% percentiles, unless otherwise stated. Changes in average pain intensity (VAS), CPI, MPQ, and SCL-90R scores, and in PPT, PPTol, and pain relief were analyzed for statistical significance with 2-way repeated measures analysis of variance (RM ANOVA) with treatment (BTX-A or saline) and time (baseline, 1 month, and 3 months) as factors. The Holm–Sidak method for pairwise multiple comparison vs a control group was used as a post hoc test when the ANOVA indicated significance. For data on ordinal scales (eg, DP, palpation count, and frequency of analgesic use), RM ANOVA on ranks (Friedman test) was used with Dunn's method for multiple comparisons vs a control group as post hoc test. The number of patients whose pain responded to BTX-A and saline as well as to the first and second injection, and the number who showed any global improvement were compared with McNemar's test.

### 3. Results

#### 3.1. Patient characteristics

Table 1 lists patient characteristics. Most patients were women of Scandinavian ethnicity, and they were married or living with a partner. No Swedish participants were unemployed, but approximately 20% were on sick leave or had a sick pension (the Danish version of the RDC/TMD does not query occupation). Educational level was high; approximately 40% had a university degree.

**Table 1**

Patient characteristics of 21 patients with myofascial temporomandibular disorders.

Characteristic	n	%
Age (y)		
Mean (SD)	38 (12)	
Gender		
Female	19	90.5
Ethnic origin		
Scandinavia	18	85.7
Other European countries	1	4.8
Middle East	2	9.5
Education		
Elementary school	4	19.0
High school	6	28.6
University	8	38.1
Occupation (n = 14) <sup>a</sup>		
Employed	6	28.6
Student	3	14.3
Retired	1	4.8
Sick leave/pension	4	19.0
Marital status		
Married/partner	18	85.7
Single	3	14.3

<sup>a</sup> This information is not included in the Danish version of the RDC/TMD questionnaire, so data are presented for the Swedish patients only.

Fifteen patients (72%) reported bilateral jaw pain, 2 reported pain on the right side only, and 4 reported pain on the left side only. Eighteen patients (86%) reported continuous and 3 intermittent jaw pain. Pain duration ranged between 6 months and 20 years, with an average of 6.3 (SD 4.7) years. Sixteen patients (76%) reported pain from other bodily locations. The most frequent locations were shoulders (12 patients) followed by neck (8 patients), back (5 patients), and back of head (3 patients). Two patients reported pain in the arms and 2 in the legs.

Seventeen patients (81%) reported that they had joint sounds, but a clinical diagnosis of disc displacement or osteoarthritis was confirmed in only 6 patients. All but 1 patient (95%) reported jaw ache, stiffness, or fatigue upon awakening and headache during the last 6 months. Seventeen (81%) were aware of diurnal or nocturnal tooth grinding/clenching. Eighteen patients (86%) reported some limitation or avoided jaw activities because of pain. The number of limited activities varied between 0 and 9, with a median (IQR) of 4 (4).

After examination, a diagnosis of myofascial pain was confirmed in all patients, 8 (38%) with limited opening. Twelve patients had myofascial pain alone; 3 also had arthralgia; 2 also had osteoarthritis; 3 had a combination of myofascial pain, disc displacement with reduction, and arthralgia; and 1 patient had a combination of myofascial pain, osteoarthritis (right temporomandibular joint), and osteoarthritis (left temporomandibular joint).

Fifteen patients (71%) received analgesics for their jaw pain. Peripherally acting analgesics, such as nonsteroidal anti-inflammatory drugs and acetaminophen, were most commonly administered (7 patients each), while 2 patients received salicylic acid. Three patients received a combination of acetaminophen and codeine, 1 received tramadol, 1 received gabapentin, and 1 patient each received venlafaxine, mirtazapine, or citalopram.

#### 3.2. Treatment compliance and side effects

Twelve patients received BTX-A as the first injection and 9 received saline. Most patients completed the study; only one dropped out. This patient completed the first half of the study (BTX-A injection) but did not come to the follow-ups after the



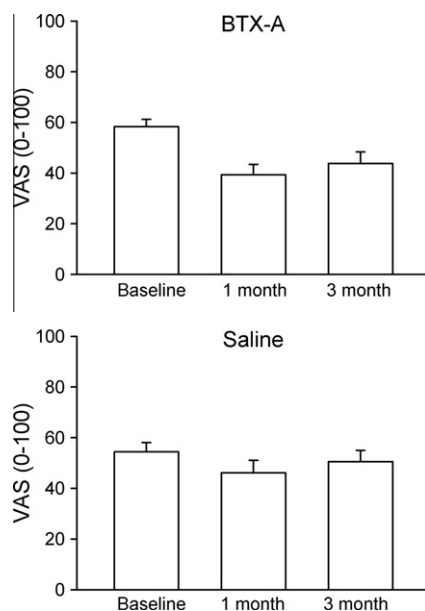
second injection (saline) because of lack of effect of the injections. Another patient came to all visits apart from the 3-month follow-up after the second injection (saline) because of lack of effect of this latter injection. But she did complete all questionnaires, and we retrieved data for our primary and secondary outcome measures for all follow-up visits (only the clinical examination was incomplete). We therefore did not regard her as a dropout.

Side effects reported by the patients the first week after injections were frequent and of varying intensity but unrelated to drug. The most frequently reported side effect was headache, which 7 patients reported after BTX-A and 9 patients after saline. Two patients reported tiredness or fatigue after BTX-A, ie, symptoms that could be interpreted as muscle weakness, while 4 patients reported this after saline. Three patients reported jaw pain after BTX-A, compared to 1 after saline. Influenza-like symptoms were reported by 2 patients after BTX-A and 1 patient after saline. One subject reported dry mouth after BTX-A. All side effects had resolved at the 1-month follow-up.

### 3.3. Pain variables

Least baseline pain intensity (mean and SD), assessed during 1 week before examinations was 34 (18) for BTX-A and 31 (20) for saline, while worst baseline pain intensity was 80 (14) for BTX-A and 74 (19) for saline. Average pain intensity at baseline was 58 (13) for BTX-A and 54 (17) for saline. The average baseline intensity before the first injection, independent of type, was 58 (14) and before the second injection 55 (16)—that is, there were no carryover effects that were dependent on whether BTX-A or saline was provided as the first injection.

Fig. 2 illustrates average weekly pain intensity at baseline and at the 1- and 3-month follow-ups. There was no between-drug difference in average weekly pain intensity (2-way RM ANOVA;  $F_{1,37} = 2.076$ ,  $P = .163$ ), but a time effect was observed ( $F_{2,37} = 9.305$ ,  $P < .001$ ). The post hoc test showed a significant reduction in pain intensity at the 1- and 3-month follow-ups (Holm–Sidak;  $P < .017$  and  $P < .025$ , respectively). There was no



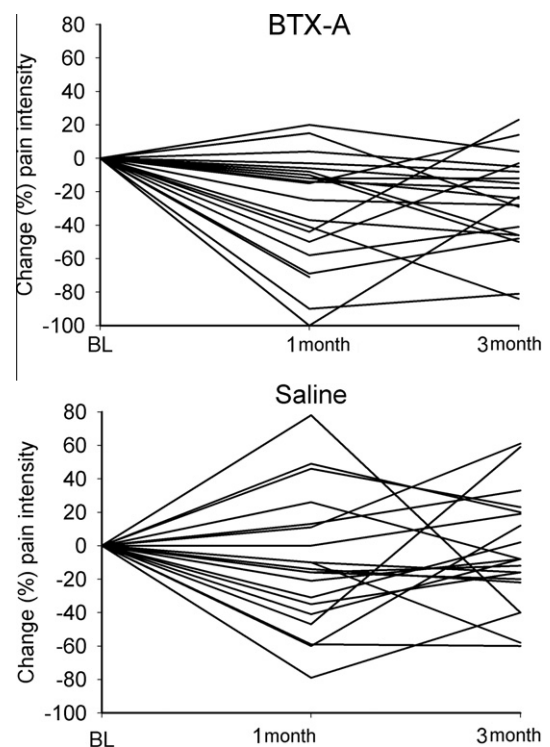
**Fig. 2.** Bar graph (mean and SEM) showing the average facial pain intensity assessed 1 week before treatment and follow-ups at 1 and 3 months after botulinum toxin type A (BTX-A) and control (saline) injections in 21 patients with myofascial TMD. Two-way RM ANOVA did not reveal any significant differences between or within groups.

interaction between drug and time ( $F_{2,37} = 2.367$ ,  $P = .108$ ). At the group level, at the 1-month follow-up, average percent pain reduction after BTX-A (mean and SD) was 30 (33%) and after saline 11 (40%). At the 3-month follow-up, pain reduction was 23 (30%) after BTX-A and 4 (33%) after saline. When individual pain reduction was calculated in an intent-to-treat analysis, 9 (43%) patients reported a 30% pain reduction after BTX-A administration compared to 7 (33%) patients after saline administration (McNemar's test; NS) at the 1-month follow-up, while 7 (33%) patients showed a 30% pain reduction after BTX-A and 4 (19%) after saline at the 3-month follow-up (NS) (Fig. 3). The number needed to treat calculated as an intent-to-treat analysis on a 30% pain reduction was 10.5 after 1 month and 7.0 after 3 months in favor of BTX-A. Six patients (29%) reported a 50% pain reduction at the 1-month follow-up after BTX-A, compared to 3 (14%) after saline (NS). At the 3-month follow-up, 3 patients (14%) reported a 50% pain reduction after BTX-A and 2 (10%) after saline (NS). The number needed to treat values calculated for a 50% pain reduction were 7.0 and 20.8 after 1 and 3 months, respectively.

We also tested whether there were any order effects of treatments. Four patients experienced a 30% pain reduction only after the first injection, 4 only after the second injection, 4 after both injections, and 8 after none of the injections at the 1-month follow up (NS). The corresponding figures after 3 months were 2, 2, 2, and 14 patients (NS).

CPI decreased significantly after treatment (2-way RM ANOVA;  $F_{2,33} = 4.312$ ,  $P = .019$ ), but without any significant difference between drugs ( $F_{1,33} = 2.744$ ,  $P = .111$ ) or interaction between time and drug ( $F_{2,33} = 1.129$ ,  $P = .336$ ) (Table 2).

The patients used all 15 descriptors of pain quality from the MPQ. The most commonly used descriptors at the first visit (before any injection) were “heavy” and “cramping” (16 patients), followed by “tender” (15 patients), and “aching” (15 patients). The least commonly used descriptors were “sickening” (2 patients)



**Fig. 3.** Individual changes (%) from baseline in pain intensity at 1 and 3 months in 21 patients with myofascial TMD treated with BTX-A and control (saline) injections of the masseter muscle.

**Table 2**  
Pain variables, physical (disability points) and emotional functioning (SCL-90R) and clinical variables at baseline and 1 and 3 months after treatment with BTX-A or control (saline) in 21 patients with myofascial TMD.<sup>a</sup>

Variable	BTX-A			Saline		
	Baseline	1 month	3 month	Baseline	1 month	3 month
<i>Characteristic pain intensity (0–100)</i>						
Mean (SD)	69 (11)	61 (15)	58 (14)	67 (14)	65 (15)	65 (11)
<i>Pain relief (0–100)</i>						
Mean (SD)		35 (35)	34 (36)		27 (29)	24 (29)
<i>McGill pain Questionnaire</i>						
Sensory (0–33)						
Mean (SD)	10.8 (4.2)	9.0 (6.2)	9.9 (5.7)	11.5 (5.5)	9.8 (4.7)	9.5 (4.4)
Affective (0–12)						
Mean (SD)	3.6 (2.7)	2.5 (2.6)	3.2 (2.9)	3.3 (3.8)	3.1 (3.1)	3.1 (3.0)
Total (0–45)						
Mean (SD)	14.3 (5.3)	11.5 (8.1)	13.1 (8.0)	14.9 (9.0)	12.9 (7.1)	12.5 (6.7)
<i>Disability points (0–6)</i>						
Median (IQR)	1 (3)	1 (3)	0 (2)	1 (3)	0 (3)	1 (3)
<i>SCL-90R (0–4)</i>						
Depression						
Mean (SD)	0.9 (0.5)	0.8 (0.5)	1.0 (0.7)	1.0 (0.7)	0.9 (0.7)	0.9 (0.6)
Somatization						
Mean (SD)	1.2 (0.7)	0.9 (0.6)	1.1 (0.8)	1.1 (0.7)	1.0 (0.7)	1.0 (0.6)
<i>Unassisted painfree jaw opening (mm)</i>						
Mean (SD)	42.7 (11.3)	44.3 (7.2)	44.3 (7.2)	43.4 (7.3)	44.3 (7.3)	44.2 (8.7)
<i>Palpatory pain count (0–20)</i>						
Median (IQR)	13 (8)	13 (10)	12 (7)	14 (6)	11 (6.5)	12 (6)*
<i>PPT (kPa)</i>						
Mean (SD)	112 (33)	119 (36)	111 (44)	107 (31)	121 (43)	116 (31)
<i>PPTol (kPa)</i>						
Mean (SD)	239 (92)	253 (95)	229 (95)	257 (129)	268 (128)	259 (129)

<sup>a</sup> The CPT decreased significantly after treatments, but without significant differences in time or interaction between drugs and time.

\* Significant difference compared to baseline.

and “stabbing” (4 patients). MPQ scores for the sensory and affective dimensions of pain quality, as well as the total score, are shown in Table 2. None of the scores changed significantly after any treatment.

### 3.4. Physical functioning

Nine patients reported no disability according to the Graded Chronic Pain Scale at baseline before BTX-A, 4 had mild disability (1–2 DP), 3 had moderate disability (3–4 DP), and 4 had severe disability (5–6 DP). The corresponding figures at baseline before saline injection were 7 (no), 7 (mild), 3 (moderate), and 2 (severe) patients. The DP score before and after treatment is shown in Table 2. There were no changes in DP score after any treatment compared with baseline.

### 3.5. Emotional functioning

Six patients (29%) had normal depression scores at baseline before BTX-A (<0.535) according to the SCL-90R, 9 (43%) had a moderate grade of depression (0.535–1.104), and 6 (29%) had a severe grade of depression (>1.105). At baseline before saline injection, 6 patients (29%) had normal depression scores, 6 (29%) had a moderate grade of depression, and 9 (43%) had a severe grade of depression. The depression scores before and after treatment are shown in Table 2. There were no changes in depression score after any treatment.

Three patients (14%) had normal somatization scores at baseline before BTX-A (<0.500), 6 (29%) had a moderate grade of somatization (0.500–0.999), and 12 (57%) had a severe grade of somatization (>1.000). The corresponding figures at baseline

before saline injection were 3 (14%), 7 (33%), and 11 (52%), respectively. The average somatization score did not change significantly after treatments (Table 2).

### 3.6. Global improvement

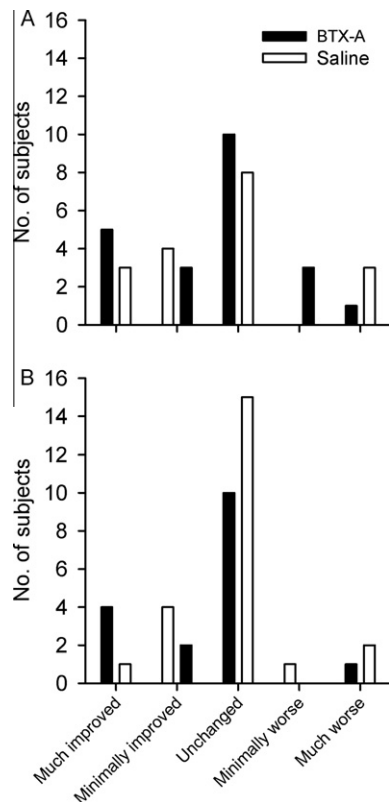
Fig. 4 shows PGIC scores at the 1-month (A) and 3-month (B) follow-ups. In general, there were modest improvements after treatments with both drugs. The number of patients reporting improvement (grade 0–2) did not differ between drugs (McNemar's test). Pain relief after treatment is shown in Table 2. There were no differences in pain relief between drugs or visits.

### 3.7. Additional outcome measures

At baseline, 6 patients received analgesics daily, 3 patients 2–3 times a week, 4 patients once a week, and 3 patients 1–2 times a month; 4 patients never used analgesics. No significant changes in frequency of analgesic use occurred after any treatment.

The mean (SD) unassisted pain-free jaw opening at the first visit (before any injections) was 38.1 (12.8) mm. Eight patients had an unassisted pain-free jaw opening of <40 mm at baseline before BTX-A injection compared to 5 patients before saline injections. Jaw-opening capacity did not change as a consequence of treatments (Table 2).

The average palpation count is shown in Table 2. No change in palpation count occurred after BTX-A, but a significant change occurred after saline administration (Friedman test;  $P = .007$ ), with a significantly lower score at the 3-month follow-up compared to baseline (Dunn's test;  $P < .05$ ). Because injections were given in the masseter muscle only, we also analyzed for treatment effects



**Fig. 4.** Perceived impression of global changes (A) 1 month and (B) 3 months after treatment with BTX-A and control (saline) injections of the masseter muscle in 21 patients with myofascial TMD. There were no significant differences between drugs (McNemar's test).

in palpatory pain of the masseter muscle separately. There were no significant changes after BTX-A, but the palpation count decreased after saline (Friedman test,  $P = .012$ ). However, the post hoc test could not determine which time point differed (Dunn's test).

The PPT and PPTol over the masseter muscles assessed at the first examination did not differ between the right and left sides (data not shown). PPT and PPTol before and after treatments are shown in Table 2. There were no significant differences between drugs or over time in these variables. Nor were there any significant differences in PPT or PPTol over the extracranial control point between drugs or times.

#### 4. Discussion

Since the US Food and Drug Administration approved Botox<sup>®</sup> for the treatment of strabismus and blepharospasm in 1989 (<http://www.fda.gov/htm>), botulinum toxins have garnered much interest and are now approved for the treatment of cervical dystonia, strabismus, and hyperhidrosis, as well as for cosmetic use [42]. It has also become increasingly common to use botulinum toxin for myofascial pain, which is mirrored in the research community. A quick search on PubMed (March 2011) using the terms "botulinum toxin" AND "myofascial pain" yielded 77 articles published since 1994. Limiting the search to RCTs, however, yields only 18 studies, and of these, only 4 concern TMD patients. Thus, the findings of the present RCT add valuable knowledge.

Our study showed no significant difference in pain reduction between BTX-A and saline injection into the masseter muscle of patients with persistent myofascial TMD. Nor were there any significant differences between BTX-A and saline regarding the effect on physical or emotional function, global improvement, or other clinical measures. Our results support previous findings from

systematic reviews concerning other myofascial pain conditions [20,38,42,63] and headaches, including tension-type headache [47]. Our results are also in line with those of 2 RCTs concerning myofascial TMD [25,36]. Only one RCT reported a clear treatment effect of BTX-A [59]. In that study, a large number of patients was included, but the study was single-blinded, which is a significant limitation.

It is noteworthy that we found that BTX-A, but not saline, had a clinically significant pain-reducing effect (30%) at the 1-month follow-up on a group level. This is similar to results found by others: Guarda-Nardini et al. [19] reported a 50% reduction 1 month after BTX-A and 5% after saline, while Kurtoglu et al. [25] reported a pain reduction (CPI) similar in magnitude to ours, 22% for BTX-A and 13% for saline at the (final) 1-month follow-up. Clinically, it is evident that BTX-A may have a pain-relieving effect that is independent of its muscle-relaxing effects, because pain relief can precede muscle relaxation and last for a longer period, and it also is present outside injected areas [1,4]. Animal studies have shown that subcutaneous BTX-A inhibits formalin-induced inflammatory pain by preventing the release of glutamate, substance P, and calcitonin gene-related peptide from nociceptive nerve endings [1]. However, the results from human experiments are inconclusive. Two studies showed no effect on thermal or electrical pain thresholds or capsaicin-induced secondary hyperalgesia by intradermal or subcutaneous BTX-A [2,58], while another study reported that intradermal BTX-A reduced capsaicin-induced flare [17].

A large variation in treatment effect occurred for both BTX-A and saline, ranging from a 100% decrease to a 20% increase in pain intensity for BTX-A and from a 78% decrease to a 78% increase for saline, but both groups demonstrated a net pain reduction at the 1-month follow-up. This indicates a considerable placebo effect. In previous treatment studies of musculoskeletal pain conditions, a placebo effect ranging 12–40% has been reported [24,33]. Our study used a crossover design, which is the strongest design because the patients are their own controls. However, the disadvantage can be patient bias resulting from expectations of treatment effect: a patient who experiences pain reduction after the first injection might expect the second injection to be less effective, and vice versa. On the other hand, we did not observe any such trends in the present study: 4 patients each experienced a 30% pain reduction after either the first or second injection; 4 patients experienced pain reduction after both injections; and the pain of 8 patients failed to respond to either injection. We thus consider this unlikely. Other explanations for the pain reduction after saline could be a needling effect [54] and regression to the mean resulting from the fluctuating course of TMD [60].

Pain, and chronic pain in particular, affects emotional function. A recent large survey in Europe reported that 21% of patients with chronic pain were also depressed [3]. Patients with TMD are no exception; several studies have reported high levels of depression and somatization in TMD patients [31,44,62]. In a multicenter study performed in 2010, a total of 21% of TMD patients had severe and 24% moderate grades of depression [32]. Our figures were higher: 43% had a moderate grade of depression and 29% a severe grade of depression. High scores were also found for somatization in our study. These results may be due to our choice of patient sample, because TMD patients with poorer treatment outcome demonstrate higher depression scores [18]. In accordance with the study of Kurtoglu et al. [25], we found no treatment effect on depression or somatization scores. Our results are also in line with those of 2 recent RCT studies on vestibulodynia and headache [39,46].

In general, patients reported a relatively low grade of functional impairment, measured as pain-related disability; about two-thirds reported no or mild limitation. This might seem surprising because the patients had quite high grades of depression and somatization,

which have been linked to grade of functional impairment [30]. However, the figures are still higher than in a previous study, where 80% reported no limitation [61]. Treatment had no effect on pain-related disability or pain-free jaw opening, which also can serve as a measure of functional impairment. None of the other outcome measures was affected by the treatments except palpatory pain, which was significantly lower at 3 months after saline injection. The reason for this finding is not clear.

Mild to moderate side effects occurred frequently after both treatments. The most common side effects reported in the literature after BTX-A include transient muscle weakness, nausea, and pruritus of mild intensity [16]. For BTX-A injections into the masseter muscle, side effects include change in facial expression and difficulties in chewing and swallowing [16,36,51,52]. Similar to previous studies, a few patients reported muscle weakness or increased pain after injections of BTX-A, but this was also found after saline injections. In contrast to the study by Nixdorf and coworkers [36], no patients withdrew from our study as a result of adverse effects. In fact, the dropout rate was very low: only one patient withdrew from the study, and this was after the second injection because of lack of effect of either injection.

To overcome some of the shortcomings of earlier studies, only patients with myofascial TMD according to RDC/TMD that had persisted despite treatment for at least 6 months and without concomitant regional or generalized musculoskeletal pain were included in this study. Although evidence for the efficacy of most TMD treatments is limited [27], the clinical impression is that most patients with myofascial TMD improve with reversible conservative treatment, such as occlusal appliances and physical therapy. Recent studies have reported a reduction in EMG activity after BTX-A treatment in myofascial pain [26,43], and we therefore speculated that patients for whom conservative treatment gives inadequate pain relief might benefit from BTX-A as an adjunct. However, the low efficacy of BTX-A, in addition to its high cost and reduced effect with repeated injections [8,9], limits its usefulness, even for myofascial TMD patients with persistent pain.

A few limitations in this study need to be addressed. First, even though this is the largest study with double-blind methodology concerning BTX-A treatment in myofascial TMD, the number of patients was still small. It was also a very select group of patients who were being treated at specialist clinics. Despite the clinically significant pain reducing effect by BTX-A, the number of patients who experienced a 30% pain reduction was not higher than for saline at any follow-up. Thus, even though the pain decreased more than for saline on a group level, efficacy was not impressive, and inclusion of more patients might not have changed this. Second, we chose to treat only the masseter muscle. It is possible that also treating other jaw muscles could have led to a better outcome. In previous studies of chronic orofacial myalgia [19,25,36,59], the masseter and temporalis muscles were injected, and in one, the medial pterygoid muscle was also injected [59], but apart from the latter study, which was single-blinded, the results are not impressive, although some pain relief was reported in 2 of the other studies. However, results of previous studies concerning other myofascial pain conditions do not support a positive treatment effect by BTX-A [20,38,42,63]. Third, we did not assess the success of blinding; there is a possibility that the better results after BTX-A could be the result of disclosure of the drug. On the other hand, the difference in success rates between drugs was minor, and in addition, there were in fact more patients who reported muscle weakness after saline injections than after BTX-A. Last, it is recommended that nonparametric statistics should be used for composite scores from questionnaires and for VAS [50], even though the VAS has ratio properties [40]. Thus, we also used nonparametric statistics for these data, but the results were

unchanged, and we decided to report only the results of parametric statistics.

Within the limitations of this study, we conclude that BTX-A is not efficacious as an adjunct to conservative treatment in patients with persistent myofascial TMD pain.

### Conflict of interest statement

The authors do not have any financial relationships that might lead to a conflict of interest.

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