

## SPINE SECTION

### Original Research Articles

# Botulinum Type A Toxin Complex for the Relief of Upper Back Myofascial Pain Syndrome: How Do Fixed-Location Injections Compare with Trigger Point-Focused Injections?

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### Abstract

**Objective.** This was a prospective, randomized, double-blind, placebo-controlled, 12-week, multi-center study to evaluate the efficacy and tolerability of fixed location injections of botulinum type A toxin (BoNT-A, Dysport) in predetermined injection sites in patients with myofascial pain syndrome of the upper back.

**Design.** Patients with moderate-to-severe myofascial pain syndrome affecting cervical and/or shoulder muscles (10 trigger points, disease duration 6–24 months) and moderate-to-severe pain intensity were randomized to BoNT-A (N = 81) or saline (N = 72).

**Intervention.** Patients received treatment into 10 predetermined fixed injection sites in the head, neck, and shoulder (40 units of BoNT-A per site or saline, a total of 400 units of BoNT-A).

**Outcome Measures.** The primary efficacy outcome was the proportion of patients with mild or no pain at week 5 (responders). Secondary outcomes included changes in pain intensity and the number of pain-free days per week.

**Results.** At week 5, 49% (37/76) of BoNT-A patients and 38% (27/72) of placebo patients had responded to treatment ( $P = 0.1873$ ). Duration of daily pain was reduced in the BoNT-A group compared with the placebo group from week 5, with statistically significant differences at weeks 9 and 10 ( $P = 0.04$  for both). Treatment was well tolerated.

**Conclusion.** Fixed-location treatment with BoNT-A of patients with upper back myofascial pain syndrome did not lead to a significant improvement of the main target parameter in week 5 after treatment. Only in week 8 were significant differences found. Several secondary parameters, such as physicians' global assessment and patients' global assessment, significantly favored BoNT-A over placebo at weeks 8 and 12.

**Key Words.** Botulinum Type A Toxin; Upper Back Myofascial Pain; Myofascial Trigger Points; Injection Technique

### Introduction

Myofascial pain syndrome is a chronic musculoskeletal disorder in which areas of intense tenderness, called trigger points, transfer pain to surrounding areas [1,2]. The pathology involved is complex and is thought to involve numerous mechanisms, including ischemia-induced muscle spasms, hyperactivity of the neuromuscular spindle or motor endplate, and peripheral or central sensory sensitization [1–8]. Treatment options include steroidal and nonsteroidal anti-inflammatory agents, antidepressants, vasodilators, injection of local anesthetics or sodium chloride, stimulation methods, and physiotherapy, although treatment reliability is low and limited by side effects [9,10].

Botulinum type A toxin (BoNT-A) possesses antinociceptive and muscle-relaxant properties, and is currently used for the treatment of chronic pain and a range of muscular disorders [11–14]. BoNT-A may modulate the activity of muscle spindles, suggesting possible efficacy in the treatment of myofascial pain syndrome [15,16], a hypothesis supported by initial, small-scale investigations [17–19]. For example, in a randomized, double-blind, placebo-controlled study, four patients receiving BoNT-A reported a reduction in pain of at least 30%—a significant improvement compared with placebo treatment [17]. Additionally, a randomized, double-blind study involving 33 patients receiving BoNT-A (50 or 100 units of BoNT-A) compared with those who received saline [18]. A third study, a single-center, randomized investigation performed in 40 patients, reported greater pain reduction in patients who received BoNT-A compared with those who received methylprednisone—the difference was statistically significantly different at 60 days post-injection [19]. BoNT-A is currently indicated for a number of conditions and is well tolerated [11,20].

This study aimed to confirm the efficacy and tolerability of BoNT-A for the treatment of myofascial pain syndrome at higher doses and in a larger patient population than earlier investigations using standardized fixed location injections in predetermined injection [17–19,21,24,25]. The compound used was Dysport, a highly purified BoNT-A-7-hemagglutinin complex that has been registered for clinical use in Europe since 1990. A concurrent study investigated BoNT-A administered as individualized trigger point-aimed injections [21]. This study followed the same design and was performed at the same time, but in different investigational centers as the individualized study [21]. The only difference in design between the two studies was the use of a standardized location injection scheme in this study compared with individualized injections.

## **Methods**

### *Study Design*

This was a prospective, randomized, double-blind, placebo-controlled, phase III multicenter study to investigate the efficacy and safety of BoNT-A administered to patients with upper back myofascial pain syndrome. The study design was identical to that reported previously by Göbel et al. [21], except that all patients received a standardized fixed-location injection scheme of BoNT-A rather than individualized trigger point-aimed injections administered into the 10 most painful trigger points [21].

Eligible patients were recruited between April 26, 2002 and April 22, 2004 at 17 hospitals and clinics based in Germany. All patients provided written informed consent prior to study enrolment. The study was approved by the Independent Ethics Committee and the institutional review board at each study site. The study was conducted in compliance with the Declaration of Helsinki (1996 amend-

ment) and the principles of Good Clinical Practice, as well as in accordance with all local regulatory requirements.

### *Patients*

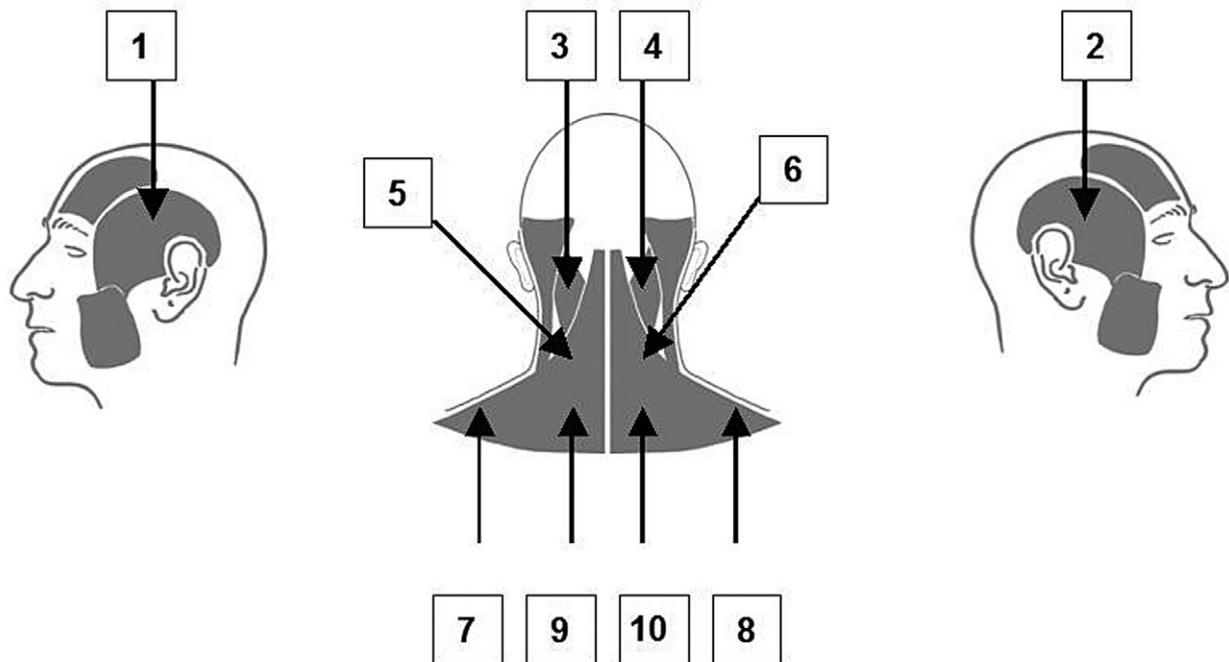
Inclusion and exclusion criteria for the study were identical to those for the study by Göbel et al. [21]. Briefly, eligibility criteria included: 18–70 years old; myofascial pain syndrome affecting cervical muscles of the back and shoulder ( $\geq 10$  trigger points, disease duration of 6–24 months) and moderate-to-severe pain intensity (defined as a mean weekly score of at least three points on an ordinal self-rating pain score rated from 1 [no pain] to 4 [severe pain]).

Patients were not eligible for study inclusion if they: 1) had received prior treatment with botulinum toxin for pain therapy; 2) had participated in another clinical trial during the 3 months prior to enrolment or at the same time as this study; 3) had concurrent muscle disease; 4) had conditions associated with congenital and/or medication-induced bleeding; 5) were pregnant or at risk of pregnancy; 6) had severe concomitant disease; 7) had a history of drug or alcohol abuse; 8) had specific back pain disorders; 9) had a body mass index  $\geq 30$  kg/m<sup>2</sup>; and 10) had used certain medications. Concomitant medications not permitted during the 4 weeks prior to treatment were: opioids; invasive therapy or neuromuscular blocks in the region of treatment; and parenteral or oral corticosteroids. During the week prior to treatment, patients were not allowed to take nonsteroidal anti-inflammatory drugs, topical anti-rheumatics, topical corticosteroids, or muscle relaxants. During the day prior to treatment, paracetamol, other analgesics, and therapy with heat, massages, rheumatism bath therapy, or treatment with cold were not permitted.

### *Randomization and Treatment*

At visit 2 (week 0), patients were randomized (1:1) to one of the two treatment blocks using a computer-generated randomization schedule. Patients received either BoNT-A (400 units of Dysport) or placebo (0.9% NaCl solution). The two solutions were identical in appearance, color, form, size, consistency, and odor. Patients and physicians were blinded to treatment. It should be noted that because of differences in the assays used, units of different BoNT-A products are not interchangeable [22,23]. Unless stated otherwise, dose specification of units in this article refers exclusively to BoNT-A, and cannot be applied to other BoNT-A preparations.

Active treatment or placebo was prepared independently at each study site by a person who was not involved in the study according to the randomization code provided in a sealed envelope. Investigators also received a sealed envelope containing the randomization code for each patient, although these were only to be opened in the event of an emergency. Randomization codes were kept at a central location and disclosed only at the end of the study once all evaluations had been completed.



**Figure 1** Standardized predetermined injection sites in the head, neck, and shoulder.

Unlike the concurrent study [21], where individualized trigger point-aimed injection sites were used, injections were administered into 10 fixed location predetermined injection sites in the head, neck, and shoulder (40 units of BoNT-A in 0.4 mL saline per site or 0.4 mL saline for placebo subjects) (Figure 1). The injections were administered with 2.5 mL syringes, using a 27-gauge 40 mm needle at a depth of 1–2 cm.

#### Assessments

At the screening visits (week 1), patients received a diary to record pain intensity each day and rated pain on a 4-point scale: 1, no pain; 2, mild pain; 3, moderate pain, and 4, severe pain. Patients kept a daily record of their pain during the week prior to randomization and for 12 weeks after treatment. Additionally, all patients underwent a physical examination, and body weight and vital signs were recorded. Following the initial treatment visit, assessments of vital signs, pain on palpitation of cervical and shoulder muscles, concomitant diseases and therapies, adverse events (AEs), and diary compliance were recorded every 4 weeks (weeks 4, 8, and 12).

The primary efficacy end point was the proportion (percentage) of patients with mild or no pain at week 5 (responders). This time point was chosen as the maximum effect of botulinum toxin injection is to be expected around 4 weeks. Secondary efficacy end points included: 1) changes in pain intensity; 2) duration of pain; 3) number of pain-free days per week; 4) duration of sleep; 5) duration of migraine and tension headache; 6) time to a reduction

in pain (all assessed from daily average of data from patient diary); and 7) the number and pain intensity of trigger points (quantified by the physician at each of the five visits). In addition, global evaluation of treatment and the preference of the patients and physicians for a repeated treatment were recorded at the end of the study.

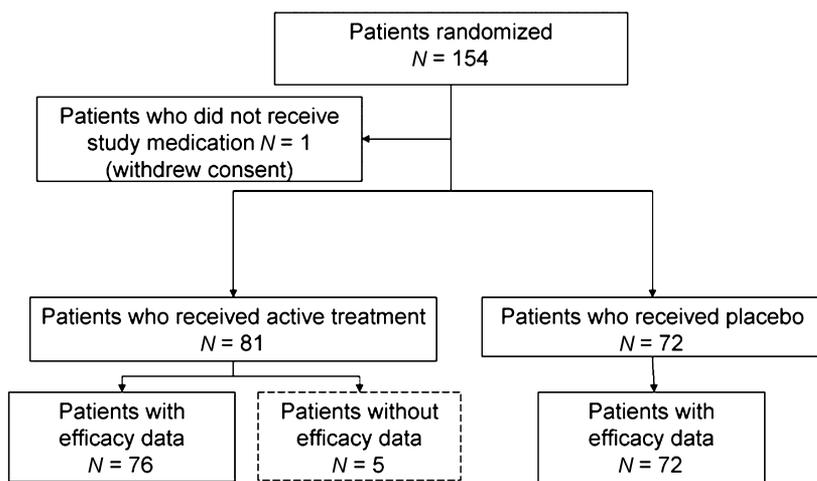
Safety assessments recorded the occurrence of any AEs and study withdrawals, monitored patients' vital signs (blood pressure, heart rate), and documented patient/physician global assessments of tolerability.

#### Statistical Methods

The study sample size was calculated assuming a difference of 30% between active treatment and placebo. In order to detect an effect with 90% power and a two-sided type 1 error of 0.05, 56 patients were required for each treatment group (N = 112 total). In order to account for possible study withdrawals, it was recommended that at least 60 patients were recruited per treatment group (N = 120 total).

Patients with efficacy data were included in the intention-to-treat (ITT) population, and those receiving treatment were included in the safety population. In the event of missing efficacy data, analyses were performed on the basis of the last observation carried forward.

Statistical analyses were performed in the same manner as for the previously reported study [21]. Briefly, continuous variables were tabulated using summary statistics,



**Figure 2** Patient flow through the study.

and descriptive statistics were calculated using the Wilcoxon rank sum test (continuous data) or the chi-squared test (frequencies and percentages). The Wilcoxon–Mann–Whitney test was used to test for baseline equivalence between the two treatment groups. Efficacy variables were analyzed with the Wilcoxon rank sum test (continuous data) or a two-tailed Fisher exact test (frequencies and percentages). All statistical tests were two-sided and performed at the 5% level of significance.

**Results**

*Patients*

A total of 154 patients were randomized to treatment (more than the 120 planned due to high recruitment frequencies). One patient withdrew consent prior to receiving any study medication. Five patients in the BoNT-A group received medication but had no efficacy data, and so were included in the safety population, but not the efficacy population. The efficacy (ITT) population consisted of 148 patients, with 76 patients receiving treatment with BoNT-A and 72 patients receiving placebo (Figure 2).

At baseline, the average height and weight of patients were lower in the placebo group compared with the BoNT-A group ( $P=0.02$  for height and  $P=0.03$  for weight). There were no significant differences between groups for any other demographic, physical, cardiovascular, or neurological characteristics at baseline (Table 1).

*Efficacy*

At week 5, 37/76 (49%) of patients in the BoNT-A group had responded to treatment compared with 27/72 (38%) of patients in the placebo group ( $P=0.1873$ ) (Figure 3). Analysis of response to treatment over time revealed that from week 4 to week 11, the number of responders was generally higher in the BoNT-A group than in the placebo group, although the difference was not statistically significant. At week 8, however, improvements in the

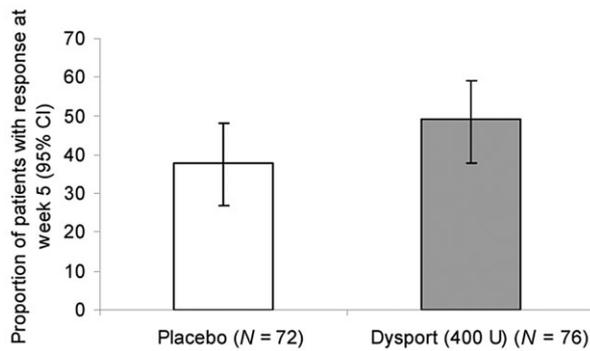
change from baseline in pain intensity over time were significantly greater for BoNT-A than placebo ( $P=0.008$ ) (Figure 4).

Duration of daily pain was reduced in the BoNT-A group compared with the placebo group from week 5, with statistically significant differences at weeks 9 and 10 ( $P=0.04$  for both) (Figure 5). Over the course of the study, there were no significant differences between groups in the duration of tension-type headaches, time per week with migraine, or the duration of sleep. Compared with patients in the placebo group, patients in the BoNT-A

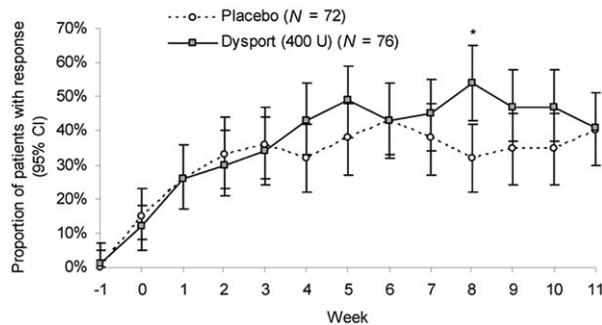
**Table 1** Baseline demographics of the patients included in the intention-to-treat population

	BoNT-A (N = 76)	Placebo (N = 72)	Difference P Value
Age (years)	48 (13)	45 (10)	0.29
Height (cm)	172 (10)	168 (8)	0.02
Weight (kg)	71 (13)	67 (13)	0.03
Sex, number of male patients	32 (42%)	20 (28%)	0.09
Systolic blood pressure (mmHg)	127 (14)	131 (12)	0.08
Diastolic blood pressure (mmHg)	78 (10)	81 (8)	0.07
Disease duration (months)	19 (8)	19 (8)	0.84
Mean weekly pain score (SE)	2.32 (0.05)	2.32 (0.04)	0.79
Suffering from tension-type headache	54 (71%)	52 (72%)	1.00
Suffering from migraine	26 (34%)	25 (35%)	1.00

Values are shown as mean (SE) unless otherwise stated. SE = standard error.



**Figure 3** Proportion of patients reporting mild or no pain 5 weeks after treatment (responders). Error bars represent 95% confidence intervals (CI).



**Figure 4** Percentage of patients reporting mild or no pain after treatment (responders) during the study course. Error bars represent 95% confidence intervals (CI).

group experienced significantly more days per week without pain at week 4 ( $P = 0.04$ ) and significantly more days per week with no or mild pain at week 8 ( $P = 0.03$ ). A Kaplan–Meier calculation of time to mild or no pain showed no significant difference between groups ( $P = 0.50$ , log-rank test).

At week 12, the mean number of trigger points had reduced from approximately 10 to approximately 9 in patients treated with BoNT-A. This was significantly different compared with the number of trigger points displayed by patients in the placebo group ( $P = 0.003$ ) that remained around 10 trigger points throughout the course of the study. In addition, pain intensity (sum of all single scores) for all trigger points was consistently significantly lower in the BoNT-A group compared with placebo from week 4 to week 12 ( $P \leq 0.001$  at weeks 4, 8, and 12) (Figure 6).

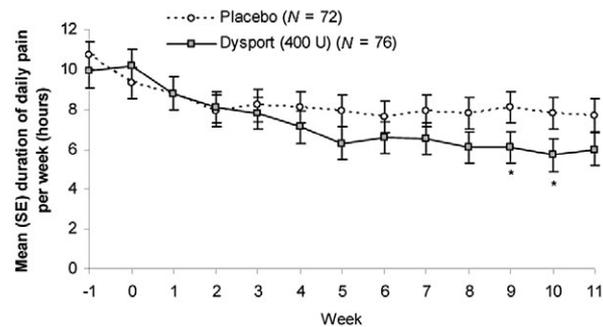
Physicians' global assessment of the patients' conditions favored BoNT-A over placebo at week 8 ( $P = 0.001$ ) and week 12 ( $P = 0.003$ ). Similarly, patients' global assessment of their conditions also favored BoNT-A over placebo at week 8 ( $P = 0.02$ ) and week 12 ( $P = 0.01$ ). There were no

statistically significant differences between the two groups in the recommendation rate for repeat treatments made by patients (54/70 [77%] BoNT-A vs. 44/71 [62%] placebo) or by physicians (59/70 [84%] BoNT-A vs. 48/71 [62%]).

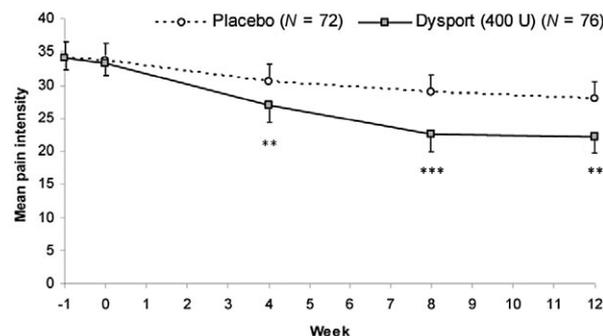
**Safety**

In total, 62 AEs were reported during the study, with no statistical differences in the number of AEs experienced by the two groups. A total of 24 patients treated with BoNT-A experienced 33 AEs among them (Table 2). In comparison, 13 patients who received placebo experienced 29 AEs among them.

The majority of AEs were mild or moderate in severity, accounting for 63% of those experienced by patients treated with BoNT-A and 69% of patients who received placebo. The most common AEs experienced by patients treated with BoNT-A were musculoskeletal, connective tissue, and bone disorders (14/33 [42%]). The most common AEs experienced by patients treated with placebo were infections and infestations (11/29 [38%]). No serious AEs occurred during the study, and no patients withdrew from the study due to AEs. In addition, assessments of vital signs throughout the study showed no



**Figure 5** Mean duration of daily pain per week (hours). Error bars represent standard error.



**Figure 6** Mean pain intensity scores for all trigger points throughout the study. Error bars represent standard error.

**Table 2** Summary of safety data

Adverse Events	BoNT-A (N = 81)	Placebo (N = 72)	Difference <i>P</i> Value
Total	33	29	—
Intensity			0.9
Mild	5 (15%)	5 (17%)	
Moderate	16 (48%)	15 (52%)	
Severe	12 (36%)	9 (31%)	
Relationship to study drug			0.02
Probable	7 (21%)	0 (0%)	
Possible	4 (12%)	1 (3%)	
Not related	14 (42%)	21 (72%)	
Not assessable	8 (24%)	7 (24%)	
Severity <sup>†</sup>			—
Serious	0 (0%)	0 (0%)	
Not serious	31 (100%)	28 (100%)	

<sup>†</sup> Analyses were not available for two patients treated with BoNT-A and one who received placebo. Percentages are calculated from the number of adverse events and do not represent the number of patients in each group.

clinically significant difference between groups for blood pressure or pulse.

## Discussion

The study results show that a standardized fixed-location treatment with BoNT-A of patients with upper back myofascial pain syndrome does not lead to a significant improvement of the main target parameter in week 5 after treatment. Only in week 8, significant differences are found. Additionally, the daily pain duration was reduced significantly at a later time, in weeks 9 and 10. The number of muscular trigger points could be significantly reduced in week 12 after treatment. The pain sensitivity of the muscular trigger points was already significantly improved from week 4 to 12. Physicians' global assessment and patients' global assessment favored BoNT-A significantly over placebo at week 8 and week 12.

In the concurrent study using individualized injections [21], significantly reduced pain levels were observed 4–6 weeks following single injections of 40 units of BoNT-A. The results from the study using individualized trigger point aimed injections would thus suggest that the administration of BoNT-A as individualized injections results in an earlier and more pronounced treatment response than administration following a standardized regimen using fixed location injections. This may be related to the more direct application of the drug to the trigger points.

In this study, almost half of the patients experienced only mild or no pain 5 weeks after treatment with BoNT-A. Unlike the study using individualized injections [21], however, this was not significantly different from that achieved in the placebo group. Improvements in response

rate, pain intensity, daily duration of pain, number of days with no or mild pain, number of trigger points, and pain intensity at trigger points were observed 8 weeks after treatment with BoNT-A and were similar to the effects observed in study using individualized injections [21]. Interestingly, the mean number of trigger points had decreased from 10 at baseline to approximately 9 by the end of this study, compared with 9.5 in the study using individualized injections [21]. In addition, patients and physicians both rated change in condition following treatment to be greater with BoNT-A than with placebo. These results were generally comparable with those from the study using individualized injections [21].

BoNT-A treatment was generally well tolerated—the majority of AEs were classified as either mild or moderate in severity and all but one resolved within 34 days of treatment. In comparison, there was a significantly higher number of AEs (specifically, neck muscle weakness) at week 4 in the study using individualized injections [21], most probably due to the higher number of injection points in the neck. No serious AEs were reported in either study.

The results reported in these two studies further add to the body of evidence for beneficial effects of BoNT-A treatment in myofascial pain syndrome [17–19,21,24,25]. In addition to the three small-scale studies that were performed prior to the initiation of this and the concomitant study using individualized injections [21], Kamanli et al. [24] reported significant reductions in pain and significant improvements in quality of life in nine patients with myofascial pain syndrome receiving BoNT-A injections (10–20 Botox® [Allergan, Irvine, CA, USA] units at three trigger points) 4 weeks following treatment. BoNT-A treatment also resulted in significantly improved levels of depression and anxiety in these patients. Furthermore, a single-center, double-blind, randomized crossover trial, in which patients first demonstrated responsiveness to bupivacaine trigger-point injection, demonstrated that both BoNT-A and bupivacaine were effective in reducing myofascial pain when compared with baseline levels ( $P = 0.0067$ ) [25].

Interestingly, a number of recent reports have failed to show a significant improvement in pain following BoNT-A treatment [26–28]. The limitations of these studies should be assessed thoroughly before comparisons are drawn, and include the use of low dose BoNT-A (total dose of 15–50 units of Botox) [26,27], short follow-up period (4 weeks) [26], and the use of concomitant pharmacologic treatment and physiotherapy in patients with low disease severity, thus limiting the ability to detect any clinical effect with the investigational agent [28]. Comparable to our data, another study reports significant improvement in cervical pain at 8 weeks but not at 4 weeks after injections [29].

The main limitation of this study was that the optimal dose and time course of treatment effects had not yet been established when the study was planned and, therefore, the dose and time points of evaluation of efficacy we selected may not have been appropriate for all patients.

Given the promising results observed using 400 units of BoNT-A in this study and the study by Göbel et al. [21] using two different injection schemes, a further dose-response study with the optimal injection pattern would help establish the most effective dose. As it is normal for the effects of BoNT-A to reduce over 12–16 weeks, it would also be useful to investigate whether a second set of injections performed toward the end of this time period would increase the therapeutic benefits observed with BoNT-A.

In conclusion, in patients with upper back myofascial pain syndrome, 10 fixed location injections of 40 units of BoNT-A (a total of 400 units of BoNT-A) produced improvements in pain control for at least 8 weeks following treatment. Although these improvements were not as substantial as those achieved using a trigger point focused injection scheme, the injections were well tolerated, and the benefits of treatment were reflected by the preferences of both investigators and patients.

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### Study Group

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The study protocol was designed by Prof Dr R. Benecke and Prof Dr H. Göbel.

### Financial Disclosure

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