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CME ARTICLE

Pericranial injection of botulinum toxin type A (Dysport®) for tension-type headache – A multicentre, double-blind, randomized, placebo-controlled study

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Increasingly, botulinum type A toxin is used to influence pathologically increased muscle activity in conditions such as dystonia and spasticity. Studies have also assessed its efficacy in tension-type headache, where muscle tenderness may be increased. We undertook a prospective, multicentre, randomized, double-blind, placebo-controlled trial. Patients received injections of Dysport® (total dose of 420 or 210 units) or saline placebo in 18 sites on the head and neck. Of 125 patients treated, 118 were included in the intention-to-treat dataset. No significant differences between each verum group and placebo were seen for the primary efficacy parameter – change in the number of headache-free days at 4–8 weeks after injection compared with 4 weeks before injection. The groups receiving 420 or 210 units of Dysport experienced 2.60 and 2.87 more headache-free days respectively, compared with 1.93 more headache-free days for the placebo group ($P = 0.66$ versus 420 units; $P = 0.52$ versus 210 units). Treatment with 420 units of Dysport was associated with significant improvements compared with placebo for two secondary efficacy parameters: mean change in headache duration from baseline to weeks 8–12 ($P < 0.05$) and improved global physician and patient assessment scores ($P < 0.05$). Further studies should address the possible value of multiple injections with extended observation periods, dose optimization, and whether duration of headache history and number of previous treatments are predictors of patient response.

Introduction

Chronic tension-type headache (TTH) evolves from episodic TTH and is classified as an average frequency of headache of more than 15 days/month for more than 3 months [1]. The pathophysiology of TTH remains largely unclear. Most hypotheses discuss a primary increased nociceptive afferent inflow, possibly caused by an increased tenderness of pericranial muscles; the resulting secondary change in the central pain threshold may be caused by either sensitization of central second-order pain neurons or decreased activity of the central antinociceptive system [2,3]. Some of these processes appear to be nitric-oxide dependent, as inhibition of nitric oxide synthetase suppresses nitric-oxide-induced headache in patients with TTH [4–6]. Such hypotheses, however, do not account for the large proportion of patients with normal muscle tone and no tenderness.

Current treatments for TTH include modulating central pain thresholds with tricyclic antidepressants or reducing muscle tenderness with muscle relaxing substances [5,7]. However, treatment is non-specific, may be ineffective in a large number of patients or some patients may develop side-effects, and there is a clear need for alternative therapies.

Increasingly, botulinum toxin type A (BoNT-A) is used to influence pathologically increased muscle activity in many conditions, particularly cervical dystonia and spasticity, with a resultant reduction also

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The authors have used the brand name throughout this report because of the potential confusion with other treatments with the same generic name: the biological effects of the products (and therefore the units used) are not the same.

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in pain [8–10]. Furthermore, *in vitro* and animal experiments provide evidence that peripheral inhibition of neuropeptide release from sensory neurons because of BoNT-A inhibits peripheral sensitization of nociceptive neurons [11]. Promising results of the efficacy of BoNT-A in patients with TTH have been obtained from small studies [12–14]. To further investigate the efficacy and safety of BoNT-A injections in chronic TTH, we performed a prospective, multicentre, randomized, double-blind, placebo-controlled trial.

The preparation used in our study, Dysport® (Ipsen Ltd, Slough, UK), is a highly purified Clostridium botulinum type A toxin–haemagglutinin complex, formulated as a vial containing 500 mouse LD_{50} units of Dysport and with a protein load of 0.87 ng/100 units of Dysport. Because of differences in assay methodology, the units of different BoNT-A compounds are not the same: 2–3 units of Dysport are approximately equivalent to 1 unit of Botox® (Allergan Inc., Irvine, CA, USA) [15,16]. This should be remembered when comparing results from studies using different compounds.

Methods

Study design

This prospective, multicentre, randomized, double-blind, placebo-controlled trial was conducted at 19 study sites in Germany. Ethics committee approvals were obtained, and the study was conducted in accordance with the Declaration of Helsinki 1996 and the Drug Law of the Federal Republic of Germany (Arzneimittelgesetz). Written consent was obtained from all patients.

The study lasted from week −6 to week 12, with six study visits (weeks −6, −4, 0, 4, 8 and 12). Following a 6-week run-in phase (weeks −6 to 0), patients who still met the inclusion criteria were randomized before the start of treatment at week 0. Patients were randomly allocated 1:1 Dysport: placebo; two Dysport doses (420 or 210 units) were used to provide additional information. Patients then entered a 12-week assessment phase (weeks 0–12).

Patients kept a daily headache diary throughout the study, completed a questionnaire at five of the six visits (weeks −4 to 12) and recorded the severity of pericranial muscle tenderness (scale of 1–4 [1, no pain; 4, severe pain and strong withdrawal] [17]) from the start of the run-in phase to the end of the assessment phase. From baseline to week 12, they also recorded the side-effects experienced. Electrophysiological examinations and biofeedback were not performed.

Inclusion and exclusion criteria

To be eligible for inclusion, patients aged 18 years or older were required to have chronic TTH, as defined by the International Headache Society (IHS) [18] at the time of the study: headache of ≥4 h for at least 15 days/month over a minimum of 6 months with two or more of the following headache characteristics – tightness; pressure or dull ache; mild-to-moderate pain intensity; bilateral location; no worsening during physical activity; no vomiting; mild photophobia, phonophobia or nausea; and no known physical or neurological basis for headache. No prophylactic medication was permitted during the study and previous prophylaxis must have been discontinued 6 weeks before randomization. Pain relief was permitted during the study, but this was limited to one pain-relief agent of the patient's choice and was recorded in the headache diary. Patients had to be capable of differentiating between TTH pain and migraine attacks.

Patients were not eligible for study inclusion if their headache diagnosis was unclear, if they had more than one migraine attack per month or if they had migraine with aura. Prior treatment with botulinum toxin in the head and neck area, and a known allergy to or antibodies against botulinum toxin were also criteria for exclusion. Participation in the study was not permitted if patients had muscular or neuromuscular disorders, or evidence of current or past drug or alcohol abuse (for analgesics and sedatives this was defined as administration on more than 10 days/month). Patients who were taking aminoglycoside antibiotics or other medications that affect the neuromuscular junction, antidepressants, neuroleptic agents, antiepileptic drugs or anticoagulants were not included in the study. Women who were pregnant or not practising an efficient method of contraception were also excluded. Acupuncture, homeopathic treatments, autogenic training (including self-hypnosis) and sports activities were permitted if their use remained constant for 3 months prior to and throughout the study.

Preparation and administration of treatment

The doses of Dysport were prepared in an investigator-blind manner by a person not otherwise involved in the study. For patients receiving 420 units of Dysport, one vial of Dysport was reconstituted with 2.5 ml of 0.9% NaCl to present a solution containing 200 units/ml. For patients receiving 210 units of Dysport, 5 ml of 0.9% NaCl was used, presenting 100 units/ml. The placebo was 0.9% NaCl solution. As this was not primarily conceived as a dose–effect study, randomization was performed in blocks of two for placebo and Dysport;

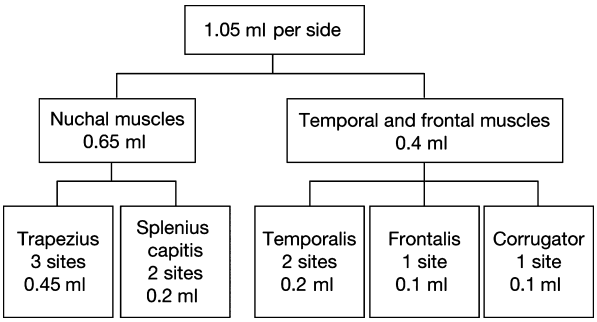

Figure 1 Summary of injection volumes and injection sites – one side of the head only.

the dose applied being further randomized within the Dysport block.

Injections were given with a 1-ml syringe and a 27- or 30-gauge needle, and without electromyographic control. Eighteen injection points were selected, nine on each side of the head. In all three treatment arms, 1.05 ml of solution was injected in each side (Fig. 1), giving a total injection volume of 2.1 ml.

Efficacy and safety assessments

Intensity of headache was recorded on a verbal rating scale of 0–3 (0, no headache; 3, severe headache) and the daily duration of headache was recorded approximately at 20:00 h every evening. Night-time hours when patients would normally be asleep were not included in the assessment of pain.

The primary efficacy parameter was the mean intra-individual change in the number of headache-free days per month from the 4-week period prior to baseline (weeks −4 to 0) to the period 4–8 weeks after injection; on a headache-free day, patients should not have experienced any headache of any duration. Secondary efficacy parameters included the mean number of headache-free days (weeks 8–12 versus baseline), mean duration (h) of headache over 4 weeks (weeks 4–8 and 8–12 versus baseline), Total Tenderness Score on palpation of pericranial muscles [verbal scale of 1–4 (1, no tenderness; 4, strong pain)], need for analgesics during the study, interference of chronic headache with daily life (evaluated by questionnaire), degree of depression (Beck's depression score at weeks −6 and 12), global assessment by physician and patient (Fig. 5) at week 12 (much better, somewhat better, unchanged, somewhat worse and much worse), and views of doctors and patients at week 12 as to whether they would continue with the treatment.

All medical complaints received from patients during the study were recorded: adverse events (AE) were reported spontaneously and in answer to specific questions at regular visits after treatment; these questions included asking if patients had suffered any dysphagia, ptosis, dysarthria or neck muscle weakness. The time of onset, duration and frequency were recorded for all AE.

Statistics

The study had an 80% power to detect a difference at the 0.05 significance level between the treatment and placebo groups in the primary efficacy end-point. A reduction in headache duration of 50% in the treatment groups or 30% in the placebo group was considered to be clinically relevant. The Mann–Whitney *U*-test was used to compare headache reduction in the BoNT-A and placebo groups, with a significance level of 0.05. The superiority of BoNT-A over placebo in the target parameters was calculated using the Wilcoxon–Mann–Whitney *U*-test with 95% confidence interval (CI); 90% CI were used for baseline parameters.

Results

Patient characteristics and disposition

In total, 125 patients were eligible for the study and received Dysport (420 units: $n = 28$ and 210 units: $n = 33$) or placebo ($n = 64$) at week 0 (Fig. 2). All patients who received a set of 18 injections at week 0 were included in the safety dataset ($n = 125$). In accordance with the principles for clinical trials [19], seven patients who underwent injections were excluded because of missing post-treatment data (headache diary entries), one of whom also chose to withdraw from the study before completion; the intention-to-treat (ITT) dataset thus comprised 118 patients. Three patients in the ITT group had significant protocol violations, leaving a per-protocol dataset of 115 patients. There were no significant differences amongst groups in the reasons presented for non-completion of the study ($P \geq 0.18$).

At baseline, patient characteristics were well-matched amongst groups, with no significant differences in headache characteristics or in the frequency or intensity of accompanying symptoms (Table 1). The vast majority of headaches were bilateral, regardless of whether the pain was frontal, parietal or occipital. Overall, patients most commonly described their headache characteristics as 'oppressive' (tightness or pressure, 89%) or 'dull' (61%). Other descriptors included 'pulling' (aching), 'sharp' and 'pulsing', reported by 19%, 17% and 15% of patients respectively.

Previous pharmacological and non-pharmacological treatments for headache, and monthly analgesic use were also comparable amongst groups (Table 1).

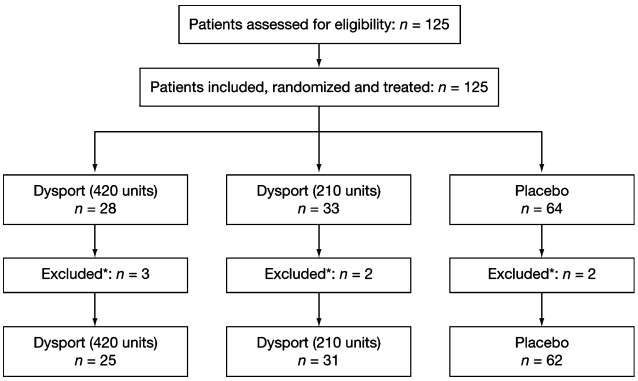

Figure 2 Flow chart of patients through the study. *Incomplete headache diaries (missing primary end-point).

Table 1 Patient and symptom characteristics at baseline (ITT dataset, descriptive statistics)

Characteristic	Dysport 420 units (n = 25)	Dysport 210 units (n = 31)	Placebo (n = 62)	P-values
Median age, years (range)	44 (20–69)	39 (21–68)	42 (19–66)	0.32
Male:female, %	44:56	44:56	48:52	0.94
History of chronic TTH, mean (SD) years	13 (13)	12 (8)	12 (12)	0.84
Frequency and duration of headache*				
Daily duration of headache, mean (SD) hours	12 (4)	14 (6)	13 (5)	0.51
Episodes per week, mean (SD)	6 (1)	6 (1)	6 (1)	0.23
Days with headache per month, mean (SD)	27 (4)	25 (6)	26 (7)	0.55
Predominant intensity*				0.80[†]
Mild	2 (8)	3 (12)	4 (7)	
Moderate	18 (72)	16 (62)	45 (75)	
Severe	5 (20)	7 (27)	11 (18)	
Headaches worsen during physical activity*	6 (24)	6 (23)	18 (31)	0.68
Accompanying symptoms (occasional)				
Aura[a]	1 (4)	4 (13)	4 (7)	0.42
Nausea[a]	3 (13)	6 (19)	15 (25)	0.45
Vomiting[a]	0 (0)	2 (6)	1 (2)	0.26
Photo- or phonophobia[b‡]	8 (33)	11 (35)	20 (32)	0.23
Previous medical or non-medical treatment for headache				
Amitriptyline[c]	15 (60)	17 (65)	33 (55)	0.66
Valproic acid[d]	1 (5)	1 (4)	2 (4)	0.96
Other pharmacological agents[c]	18 (75)	25 (93)	50 (83)	0.23
Relaxation techniques/self-hypnosis/sport[e]	15 (60)	13 (48)	31 (51)	0.66
Constant use of treatment in past 3 months[f]	22 (92)	18 (72)	42 (74)	0.16

Data are for number of patients (%) unless otherwise specified.

*Differences calculated using chi-square test; [†]combined data for all intensities; [‡]all entries recorded as 'occasional' apart from placebo (additional two patients responded 'yes'); missing data for: [a]two patients; [b]one patient; [c]seven patients; [d]17 patients; [e]five patients; [f]12 patients.

ITT, intention-to-treat; TTH, tension-type headache.

Physical examination found no statistically significant difference amongst groups in blood pressure, weight, height, neurological testing or depression scale.

Testing of pooled values for verum versus placebo found that almost all baseline characteristics were similar amongst groups. There was a non-significant difference between the BoNT-A and the placebo groups in the frequency of headaches per week (0.426; 90% CI 0.336–0.517), and in diastolic blood pressure (0.444; 90% CI 0.351–0.536). The number of days per month with headache was similar between the two groups (0.458; 90% CI 0.367–0.548). Compliance during the study was good, with over 80% of patients attending follow-up visits within the specified time frame.

Efficacy

Primary efficacy

The primary efficacy parameter was the difference in the number of headache-free days during weeks 4–8 compared with weeks−4 to 0, based on diary entries (ITT dataset). The null hypothesis – that there would be no

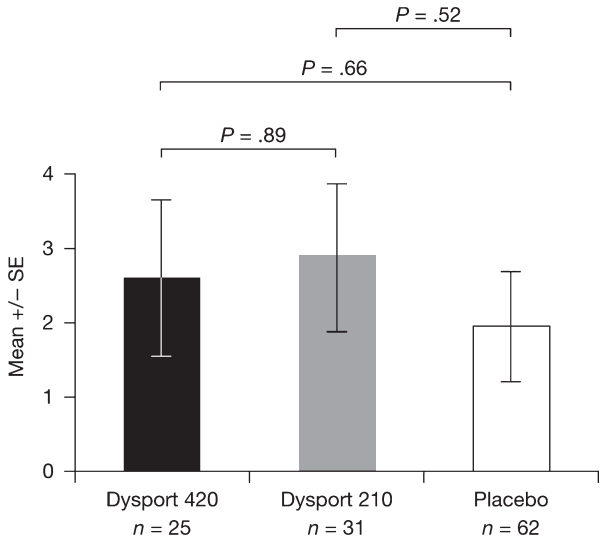

Figure 3 Change from baseline (weeks −4 to 0) in headache-free days during weeks 4–8.

significantly greater increase in headache-free days with verum than with placebo – could not be rejected. Patients receiving 420 or 210 units of Dysport experienced 2.60 and 2.87 more headache-free days respectively, compared with weeks−4 to 0 (Fig. 3), and patients receiving placebo experienced only 1.93 more headache-free days; the differences between verum and placebo were not statistically significant ($P = 0.66$ versus 420 units of Dysport; $P = 0.52$ versus 210 units of Dysport).

Secondary efficacy

The secondary outcomes are detailed in Table 2. The mean reduction in headache duration for 420 units of Dysport was 1.5 h (from 9.9 h for week −4 to week 0 to 8.4 h for weeks 8–12) compared with reductions of 0.4 and 0.2 h with 210 units of Dysport and placebo respectively. Descriptive statistics showed that the mean change in headache duration from baseline compared with weeks 8–12 was significantly higher with 420 units of Dysport than with placebo ($P < 0.05$) (Fig. 4).

There was a marked similarity between the scores for global assessment by physicians and by patients (Fig. 5). For the group that received 420 units of Dysport, physicians most commonly considered patients to be 'somewhat better' (50%) or 'much better' (21%). Patients, meanwhile, most commonly considered themselves to be 'somewhat better' (36%) or 'much better' (36%). In contrast, the modal response was 'unchanged' in both other groups, whether scored by physicians or patients. There was a significant difference in this variable between patients who received 420 units of Dysport and those who received placebo ($P < 0.05$ in both physician and patient assessments).

At the end of the treatment, 75% of physicians and 80% of patients stated that they would recommend the 420 unit dose of Dysport. The percentages of physicians and patients who would recommend the 210-unit dose of Dysport (57% and 60% respectively) and who would recommend placebo (57% and 61% respectively) were similar. The difference between the treatment groups was not significant in the physician or patient assessments.

Tolerability

Side-effects were reported more frequently in patients taking Dysport than in those receiving placebo, with a significantly different frequency of AE between pooled Dysport doses and placebo at week 4 ($P = 0.02$) and week 12 ($P = 0.02$, Table 3). Only two serious AE were reported: a patient who received 210 units of Dysport fainted and lost consciousness during an injection and a patient receiving placebo underwent a hernia operation; neither AE was considered related to therapy.

During the entire post-injection study period (weeks 0–12), only the frequency of weakness in neck muscles was significantly greater with Dysport than with placebo ($P = 0.039$, Fisher's exact test), occurring in 18% and 6% of patients who received 420 and 210 units of Dysport respectively, and in 2% of placebo recipients. Weakness of neck muscles in patients receiving 420 units of Dysport was most common in the 4 weeks directly following the injection (18% of patients), and subsided (to 11%) in weeks 4–8 and 8–12. Dysphagia occurred in 7% of the patients receiving 420 units of Dysport and in 2% of those receiving placebo; ptosis occurred only in patients receiving 420 units of Dysport (4%). All side-effects were mild to moderate and resolved within 2–4 weeks without any treatment.

Discussion

Although there was no significant difference amongst the groups in the primary efficacy parameter of change in the number of headache-free days in the period 4–8 weeks after injection compared with weeks −4 to 0, a number of secondary efficacy variables improved under verum, including mean headache intensity, analgesic use and further recommendation of the treatment. There also appeared to be a dose relationship, as these changes were greater with the higher dose, significantly so for reduction in mean headache duration and global assessment of the treatment. Interestingly, despite the higher incidence of side-effects in patients who received 420 units of Dysport, more patients and physicians

Table 2 Secondary efficacy parameters

Parameter	Dysport 420 units	Dysport 210 units	Placebo
No. headache-free days			
At weeks 8–12, mean days	5.2 (1.3)[a]	6.2 (1.4)	4.8 (0.9)
Change from weeks baseline to weeks 8–12	−2.7	−3.4	−1.7
Headache duration			
At weeks 8–12, mean hours per day	8.4 (0.9)	11.0 (0.9)	11.2 (0.7)
Change from weeks baseline[b] to weeks 8–12	−1.5[c]	−0.4	−0.2
Headache intensity pain score			
At weeks 8–12, mean	1.6 (0.1)	1.7 (0.1)	1.9 (0.1)
Change from weeks baseline to weeks 8–12	−0.2	−0.2	0.0
Depression score			
At week 12, mean	3.3 (0.9)	5.2 (1.0)	5.2 (0.6)
Change from week −6 to week 12	−0.8	1.3	−0.7
Patients reporting current headache, %			
At week 12	54	77	72
Change from week –6 to week 12	−30	−12	−17
Days per 4-week interval when analgesics were required, mean days			
During weeks 8–12	3.0 (0.7)	3.4 (0.9)	4.4 (0.7)
Change from weeks baseline to weeks 8–12	−0.6	−1.2	0.7
Total tenderness score[d]			
At week 12, mean	15.3 (0.8)	16.6 (1.1)	17.9 (0.8)
Change from week −6 to week 12	−1.3	−0.2	0.4
Patients reporting symptoms on global rating as, %			
Improved	72[e]	43	40
Unchanged	24[e]	53	54
Worse	4[e]	3	5
Patients who would recommend treatment to others, %	80	60	61

[a](SE), standard error in brackets.

[b]Baseline was weeks −4 to 0.

[c]$P < 0.05$ for 420 units of Dysport versus placebo.

[d]Six head and neck muscles (suboccipital, posterior cervical, upper trapezius, masseter, sternocleidomastoideus and temporalis) were palpated bilaterally and assigned a score of 1–4 (0, no pain, 2, slight pain and no withdrawal; 3, moderate pain and slight withdrawal; 4, strong pain and strong withdrawal or statement by the patient that the palpation induces typical headache). Individual scores were added.

[e]Group values $P < 0.05$ for 420 units of Dysport versus placebo.

would recommend this treatment than 210 units of Dysport or placebo. This surprising result may indicate that Dysport has a pain-relieving effect that was not detected by our end-points. Follow-up data would certainly be helpful to assess whether additional time is needed to reduce the number of headache-free days, as suggested by the steady decline in headache duration over the 12-week observation period.

Our results do not confirm the promising data from early studies [12–14] and case reports [20]. Although a number of other studies in addition to ours have also failed to demonstrate a significant difference in the primary efficacy end-points between BoNT-A and placebo in treating TTH, improvements between verum and placebo on secondary efficacy end-points have been noted [21–26]. Only one of the six randomized, double-blind, placebo-controlled trials analysed, however, showed evidence that BoNT-A was effective in reducing headache frequency. These variable data serve to highlight some of the complexities of treating TTH with BoNT-A. In one study that used a less stringent primary effect measure than ours, had a larger patient group than many earlier studies and used the highest dose of BoNT-A presented to patients with headache to date, there was no significant difference between active treatment and placebo or any significant benefit of verum after 12 weeks of observation following injection [25]. This contradicts earlier theories that improvement might take more than 8 weeks to become manifest. The role of the placebo effect in obscuring improvements because of verum is also unclear. In the present study, the injection itself and the use of saline may have been contributory factors. Another study in patients with TTH showed that a significant proportion of patients with TTH benefited from acupuncture and even the superficial needling of non-acupuncture points [27]. In

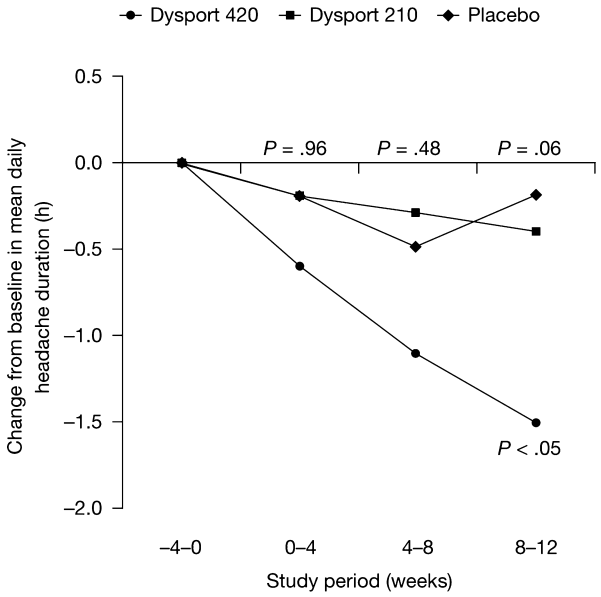

Figure 4 Difference from baseline in mean daily duration of headache. At 8–12 weeks, $P < 0.05$ for Dysport 420 units versus placebo. All other *P*-values are for pooled values of Dysport 420 and 210 units versus placebo.

contrast, however, it has been shown that dry needling did not lead to significant improvements in pain and the quality of life of patients with myofascial pain [28].

A key strength of the present study was the homogeneity of the patient population with respect to the TTH experienced. Selection according to IHS criteria ensured there were no restrictions on the duration of disease and that the definitions of headache characteristics were independent of headache history. Several limitations must also be considered, however. Firstly, the power calculation used in the development of the protocol was based on the assumption that Dysport would reduce the duration of daily headache by 50% and placebo by 30%. As the documentation by patients of headache duration was inadequate, but the occurrence of headache was always recorded, headache-free days were adopted as the new primary outcome measure. The study was thus underpowered for this measure. Secondly, it is possible that multiple injections and follow-up of at least 1 year may be required to optimize results. In a study with a 12-week, double-blind phase followed by an open-label injection of BoNT-A or placebo, the number of headache-free days did not change significantly over the initial 12-week period [29]; however, the condition of patients randomized to active treatment improved further after their second injection. In contrast to our own study, these authors used a 'follow the pain' strategy, administering injections into tender sites, rather than using predetermined injection sites. It has been suggested that the 'follow the pain'

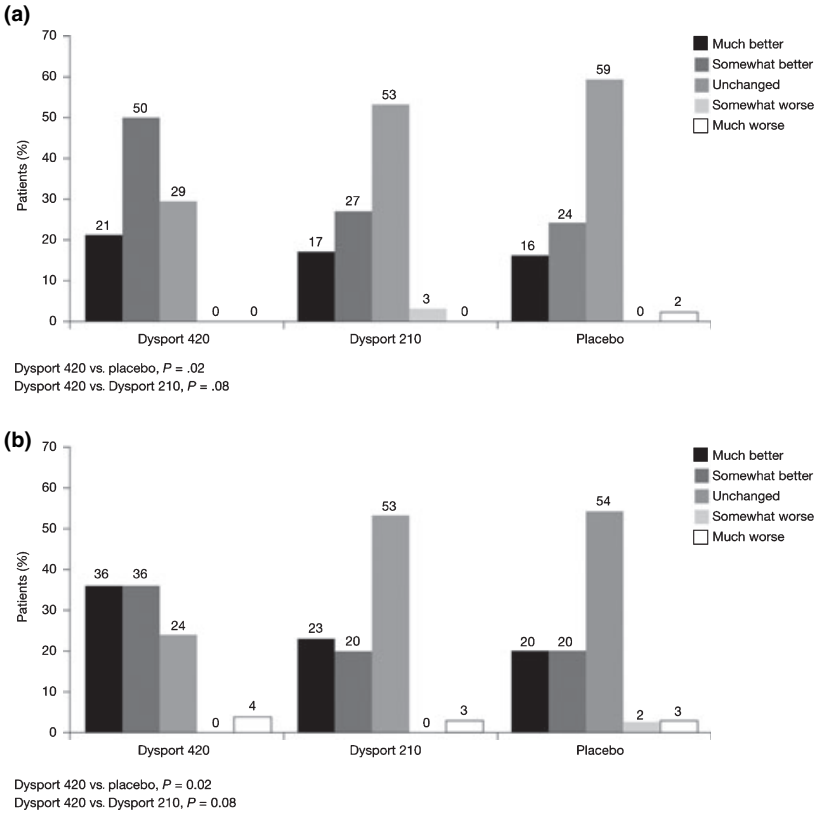

Figure 5 Global assessment scores completed by (a) physicians and (b) patients.

Table 3 Patients experiencing side-effects (safety dataset)

Reported at study visit	Percentage (*n*) of patients			
	Dysport 420 units	Dysport 210 units	Placebo	*P*-value[a]
Week 0	4 (1/28)	6 (2/33)	2 (1/63)	0.50
Week 4	23 (6/26)	27 (9/33)	7 (4/60)	0.02
Week 8	23 (6/26)	25 (8/32)	8 (5/60)	0.06
Week 12	27 (7/26)	25 (8/32)	7 (4/60)	0.02

[a]Pooled Dysport doses versus placebo.

technique, which has been used in several studies, may produce better results than a fixed-injection-site scheme [30]. The same argument, however, cannot be used to explain the findings from a 5-year study in patients with chronic daily headache [31]. Using a fixed-sites protocol, improvements in the number of headache-free days per month were accomplished after the first 3-month-treatment cycle. Nevertheless, maximum improvements were not reached until after 12 months of therapy, following multiple injections. Thirdly, in this study, a number of patients experienced neck muscle weakness, a known side-effect of BoNT-A treatment. Whilst this may have compromised the study blinding, it is difficult to avoid. Furthermore, this side-effect was also reported in the placebo group.

Chronic TTH is probably not a single disease entity. It is possible that some subgroups of patients may respond better to treatment than others. For example, an open study found that one of the predictors for efficacy of BoNT-A injections in migraine was the history of the illness – those who had experienced a longer course of illness were less probably to respond to treatment than those who had a shorter course [32]. In our study of chronic TTH, the mean history of chronic headache was 12–13 years, which might be a predictor that patients are less probably to respond to the injections.

In conclusion, our study design used a recommended primary end-point, fixed injection sites, a larger patient group and a higher BoNT-A dose than some earlier studies. Although we were unable to detect a significant difference in the primary end-point in favour of BoNT-A, improvement was seen in several secondary variables, significantly so for headache duration and global assessment of treatment. There was a tendency towards a better response with a higher dose and with a longer observation period. These observations accord with the recently published results of a larger, controlled study of chronic daily headache. Further studies could address the possible value of multiple injections, a combination of fixed injection and 'follow the pain' schemas, and the possibility that BoNT-A may be effective in specific subgroups of patients with TTH.

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Conflicts of interest

Honoraria for speeches have been received from: Allergan, Ipsen Pharma, Pfizer, Bayer, Berlin Chemie and MSD (A. Straube); Allergan, Ipsen Pharma and other manufacturers of botulinum toxin (A. Ceballos-Baumann); several pharmaceutical companies not involved in the production of botulinum toxin (T. Tölle and V. Pfaffenrath).

Study investigators

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