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The long-term efficacy and safety of botulinum toxin in refractory chronic tension-type headache

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Abstract The objective of this study was to investigate the long-term efficacy and safety of botulinum toxin type-A (BoNT-A) for refractory chronic tension-type headache (CTTH). An open-label, prospective study was carried out in the Department of Neurology of Kirikkale University on 28 patients (8 males, 20 females), mean age 35.6 years, diagnosed with moderate/severe CTTH refractory to preventive medications. Each patient received BoNT-A injections once in pericranial muscles. Efficacy and safety data were analysed for 28 refractory CTTH patients who were receiving concomitant headache prophylactic medications at baseline and during the study. The main outcome parameters were reduction of headache frequency and intensity over 1 year. Both parameters were significantly decreased ($p<0.05$) by the end of the study. Sixty-four percent of patients reported complete headache relief at the final visit, compared to 7% CTTH persisted. BoNT-A also resulted in significant reductions in analgesic consumption ($p<0.05$). Adverse effects were transient and local. BoNT-A was found to be an effective and safe treatment for refractory CTTH patients with concomitant headache prophylactic medications, resulting in significant reductions in headache frequency, intensity and analgesic consumption which persisted up to 1 year.

Keywords Botulinum toxin type-A (BoNT-A) • Chronic tension-type headache (CTTH) • Headache frequency • Headache intensity • Refractory • Treatment

Introduction

Tension-type headaches affect the majority of men and women at some time in their lives and it has a lifetime prevalence of up to 30% in the general population [1–6]. The clinical, epidemiological and societal impact of TTH is substantial, which was demonstrated in the results of a study of a Danish population which reported 870 workdays lost per 1000 people as a consequence of TTH, compared to 270 workdays lost per 1000 people for migraine [7].

Chronic tension-type headache (CTTH) is defined as the occurrence of tension-type headaches at a frequency of ≥15 days per month and is less prevalent than episodic tension-type headache [8]. However, CTTH usually evolves from the episodic form and causes significant functional impairment and morbidity [9]. Patients with CTTH exhibit poorer quality of life measures, slightly more depressive symptoms, significantly stronger avoidance behaviour and greater impairments in functioning and general well-being than patients with episodic tension-type headache [10, 11].

Botulinum toxin type-A (BoNT-A) is a focally acting neurotoxin produced by the anaerobic bacterium, *Clostridium botulinum*, which acts by interfering with acetylcholine release at the neuromuscular junction to induce temporary, reversible paralysis of the target muscle. Intramuscular injections can be administered to treat a variety of conditions such as dystonias, post-stroke spasticity, severe axillary hyperhydrosis and migraine headaches. Due to its ability to block the responses of autonomic and sensory nerves, additional applications at the central level have also been investigated (e.g., hyperlacrimation, sialorrhoea and pain conditions unrelated to muscle spasm). Recent evidence suggests that BoNT-A may reduce inflammatory pain and have distinct antinociceptive activities through inhibition of the release of nociceptive mediators [12]. With specific reference to its role in the treatment of headaches, the effectiveness of BoNT-A has been investigated in the treatment of CTTH and migraine, although a full understanding of its mechanism of action in headache continues to evolve [13–15]. CTTH differs from episodic tension-type headache in terms of frequency, lack of response to most treatment options, medication overuse and quality of life reduction. Treatment of CTTH is very difficult, with many patients failing to respond to preventive medications. Conventional treatment options comprise analgesics and prophylactic medications originally intended for conditions such as depression and epilepsy. However, the use of such medications in patients with CTTH can be limited due to lack of efficacy or unacceptable adverse effects.

The purpose of this prospective, open-label study was to assess the long-term efficacy and safety of BoNT-A treatment of refractory CTTH.

Materials and methods

Design

This study was designed to investigate the efficacy and safety of BoNT-A treatment of refractory CTTH. It comprised a prospective, open-label, one-year analysis of patients treated at the Department of Neurology.

Patients

Patients diagnosed with CTTH according to the IHS classification who were refractory to other headache medications were included in the study. All patients had received prior unsuccessful preventative and symptomatic treatments, and had been refractory to all other previous forms of headache treatment, including analgesics, non-steroidal anti-inflammatory drugs and various antidepressants. All patients had failed at least three prior treatments. All selected patients had been suffering from moderate or severe CTTH for a minimum of three years and had experienced at least 20 headache days per month. Patients with structural lesions of the brain, spine or other local or systemic diseases causing headache were excluded by appropriate laboratory studies. Informed consent was obtained prior to enrolling in the study.

Treatment protocol and outcome measures

Patients who were enrolled into the study were required to provide a detailed medical history and underwent full clinical examination prior to initiation of BoNT-A treatment. No other acute medication was administered for at least 24 h prior to baseline testing and injection of BoNT-A. BoNT-A was injected into the most affected (tender) pericranial muscles (follow the pain injection procedure). The safety of BoNT-A treatment was assessed throughout the study with the conduct of laboratory tests [e.g. complete blood count (CBC) and blood chemistries] and monitoring of any adverse events.

Patients were evaluated at baseline, and post-treatment at weeks 4 and 12, and then at one year. All patients were asked to keep a headache diary and record the number of days they experienced headaches over a period of one year and the number of days they experienced headaches judged to be sufficiently severe enough to impair or incapacitate their functional ability. Treatment with symptomatic medication was allowed on an ‘as needed’ basis for treatment of individual headaches during the study. Patients were permitted to continue with established headache prophylactic medications and the dose was stabilised more than 30 days prior to eligibility and held constant during the course of the study. Efficacy and safety data were analysed for the patients who were receiving concomitant headache prophylactic medications at baseline and during the study.

The effectiveness of BoNT-A treatment was evaluated by assessment of changes in headache frequency and intensity, as well as analgesic use. Headache intensity was defined using a 10 point rating scale [range: 0 (no pain) to 10 (worst pain imaginable)]. A physician’s global response rating assessed improvement as complete response, partial response or non-response.

Statistical analysis

Student’s *t*-test, paired *t*-test, chi square and McNemar tests were used for statistical analysis. A p value of less than 0.05 was considered to be statistically significant.

Results

A total of 28 patients [8 males (28.6%), 20 females (71.4%)] with a mean age of 35.6 years (range: 26–47 years) were enrolled and completed the study. Patients suffered a mean headache frequency of 24.9±2.9 days per month (range: 20–30 days per month), with a mean headache intensity of 7.25±1.2 according to the 10-point rating scale (range: 5–9). Mean analgesic consumption comprised 21.7±3.6 tablets per month (range: 15–27 tablets).

BoNT-A treatment

Patients were administered a mean dose of 59.5±12.1 U BoNT-A (BOTOX®) diluted in 100 U/ml saline once. The median dose was 50 U and the total dose range was 45–75 U. All pericranial muscles according to the pain injection procedure (frontalis, splenius capitis, trapezius, occipitalis and temporalis muscles) were injected.

Headache frequency

As a result of BoNT-A treatment, headache frequency was found to be significantly reduced from a mean of 24.9±2.9 days per month at baseline to 14.9±3.5 days per month by the end of week 4 ($p<0.05$), 9.1±4.8 days per month at week 12 ($p<0.05$) and 5.1±7.5 days per month by the end of the first year ($p<0.05$) (see Fig. 1). The differences in headache frequency were statistically significant between weeks 4 and 12 and between week 12 and one year ($p<0.05$).

Headache intensity and analgesic consumption

As a result of BoNT-A treatment, headache intensity according to the 10-point rating scale was found to be statistically significantly reduced from a mean score of 7.25±1.2 at baseline to 6.1±1.6 at week 4 ($p<0.05$), 2.4±3.4 at week 12 ($p<0.05$) and 2.3±3.3 by the end of one year ($p<0.05$) (see Fig. 2). The difference in intensity scores was statistically significant between weeks 4 and 12 ($p<0.05$). In addition, the mean consumption of analgesics consumed per month significantly declined throughout the course of the study (see Fig. 3).

Degree of headache frequency relief after BoNT-A treatment

With respect to improvement in the frequency of headaches based on the physician's global response rating, complete or partial response was experienced by the vast majority of patients. At week 4, 93% of patients achieved partial response, with only 7% of patients indicating having no response or a worsening of their headache frequency. At week 12, 25% of patients had complete response, 68% had a partial response and only 7% were found to have no response or a worsening of their condition. By the study endpoint at one-year post-

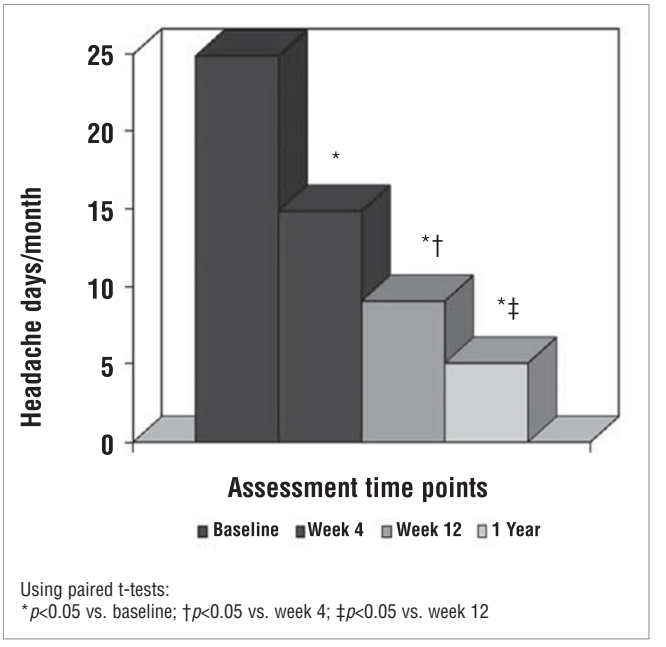

Fig. 1 Changes in the number of headache days per month following BoNT-A treatment

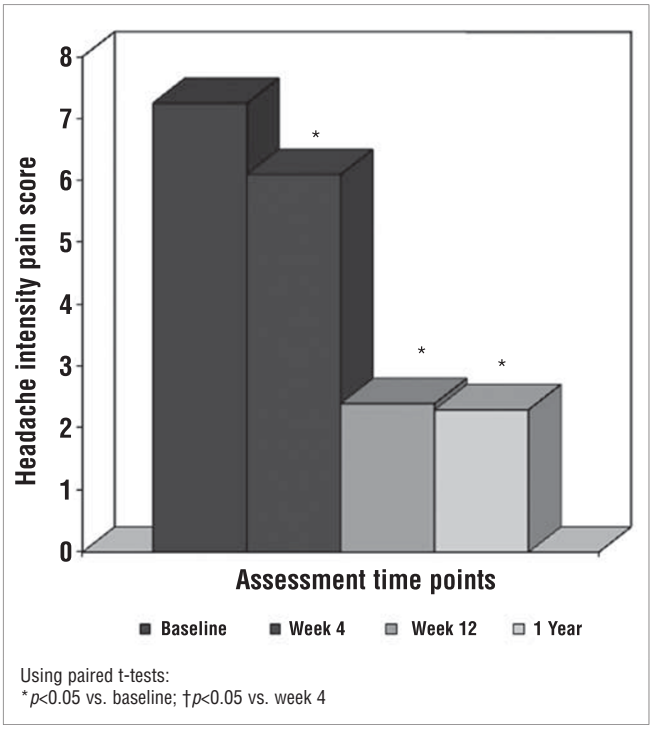

Fig. 2 Changes in headache intensity following BoNT-A treatment

treatment, 64% of patients had achieved complete response, 29% had partial response and only 7% had either no response or a worsening of headache frequency (see Table 1 and Fig. 4). Headache intensity also improved by the study endpoint in 21 of the 28 patients (75%), while three of the 28 patients (11%) experienced no change and headache intensity increased in four of 28 patients (14%) (Fig. 5).

Global outcomes

A decrease in the intensity of CTTH-associated symptoms such as nausea, vomiting, photophobia, phonophobia, vertiginous symptoms and dizziness was observed in 14 of the 28 patients (50%), while 11 of the 28 patients (40%) experienced no change and three of 28 patients (10%) reported an increase in intensity of such symptoms. No differences in response to BoNT A treatment were seen with respect to gender or age.

Safety and tolerability

BoNT-A treatment was found to be well-tolerated with the only reported treatment-related adverse event being mild, local tenderness for a few hours due to injection administration in eight patients.

Table 1 Extent of response after BoNT-A treatment

	Week 4	Week 12	1 year
	n (%)	n (%)	n (%)
Complete response	0	7 (25)	18 (64)
Partial response	26 (93)	19 (68)	8 (29)
No change or worse	2 (7)	2 (7)	2 (7)

Discussion

The results of this open-label, prospective study in 28 patients with moderate or severe CTTH demonstrated that BoNT-A is a well tolerated and effective treatment for CTTH in patients refractory to prior treatment. BoNT-A was found to significantly reduce the frequency and intensity of CTTH

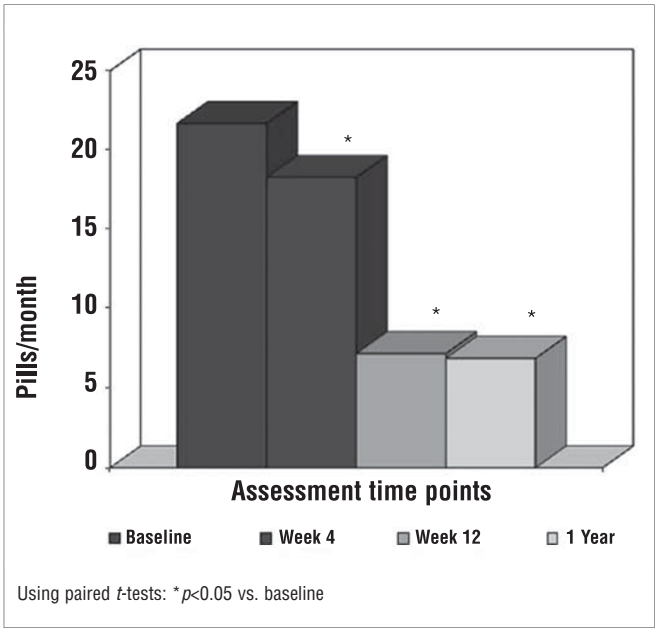

Fig. 3 Reductions in analgesic consumption following BoNT-A treatment

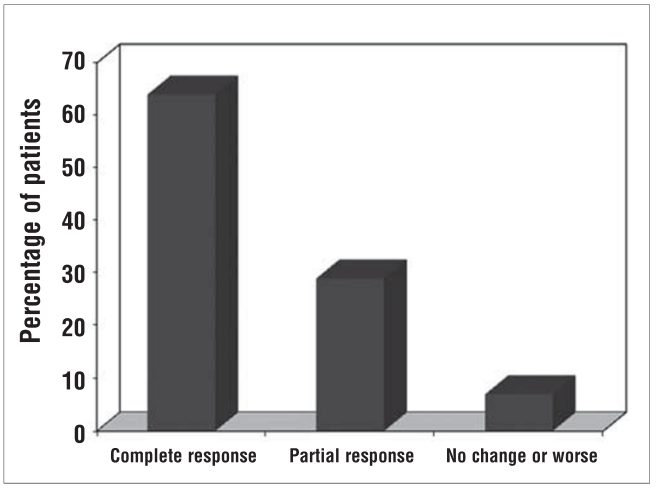

Fig. 4 Overall response to BoNT-A treatment at study endpoint (1 year), as assessed by headache frequency

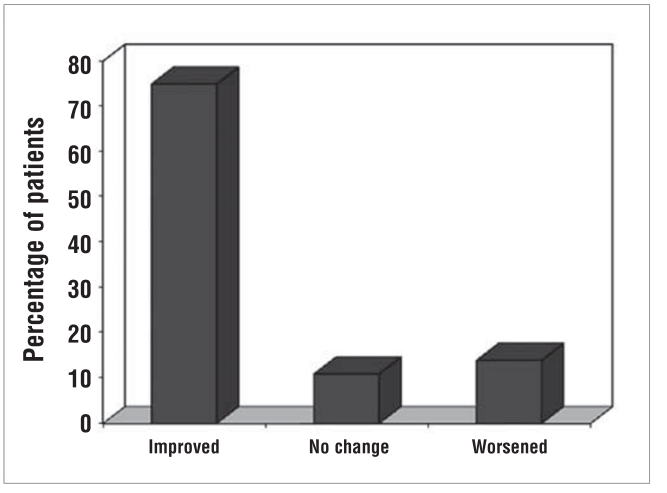

Fig. 5 Overall response to BoNT-A treatment at study endpoint (1 year), as assessed by headache intensity

for up to 1 year post-treatment. Up to 93% of patients treated with BoNT-A reported some improvement in their headache symptoms and use of BoNT-A resulted in significant reductions in analgesic consumption.

Both open and randomised, double-blind and placebo-controlled studies were performed with patients suffering from tension-type headache. Contradictory results for the efficacy of botulinum toxin were found. Relja reported a significant reduction in headache duration, pain intensity and pain sensitivity in 10 patients and found a lasting effect in long-term use over 15 months in 24 patients [16,17]. Ondo et al. reported in chronic daily headache patients that headache-free days had improved in the BoNT-A group from weeks 8 to 12 ($p<0.05$) [18]. In an open study, Schulte-Mattler et al. reported in nine patients with refractory CTTH the product of pain duration and pain intensity was significantly reduced [19]. However, several randomised, double-blind, placebo-controlled trials did not find any significant difference between Botox and placebo [20-22]. Although Burch et al. also could not show a significant difference in headache frequency between treatment with Botox and placebo, there was a significant decrease of pain intensity in the treatment group with Botox compared with the control group [23]. Smuts et al., in 37 patients with tension-type headache, reported that a trend toward decreased headache severity over the 3 months was observed in the BoNT-A-treated group. This improvement reached statistical significance at month 3 relative to the pretreatment month. Similarly, the number of headache-free days was reported to be greater at month 3 than at baseline [12]. Relja reported a prospective, randomised, double-blind trial of BoNT-A in 16 patients with CTTH who were resistant to medication. All of the patients showed reduced severity of headache, reduced pericranial muscle tenderness and increased headache-free days during BoNT-A treatment. It was reported that 94% of placebo patients still had moderate-to-severe headaches after treatment compared with only 25% (moderate only) in the BoNT-A group (75% had no or mild headaches after treatment) [24]. Besides these, Mennini et al. reported that 85% of CTTH patients experienced at least some degree of pain relief and reduced their use of analgesics after BoNT-A treatment [25]. BoNT-A therapy was reported to be an efficacious new therapeutic choice in the prophylaxis of CDH, especially for patients not responding to previous prophylactic treatments [26].

Comparisons between this study and reported studies are complicated by differences in study design (number of injection session), patient populations and the concomitant headache prophylactic medications of this study. The responses of CTTH patients to the medication, concomitant prophylactic medication and only one injection session of BoNT-A differ in our study from the others. Although there were a number of studies evaluating the prophylactic efficacy of BoNT-A in CCTH, in this study patients were CTTH who were refractory to the treatment and besides that they were permitted to continue with established headache prophylaxis medications. Although Mathew et al. conducted a randomised, placebo-controlled study to examine the effect of BoNT-A in CDH with concomitant headache prophylactic medication, there were nine CTTH patients and the results of these CTTH patients were not reported separately [27]. In our study, the possible impact of prophylactic medication use on the outcomes has not been underestimated. As the patients were refractory to the prophylactic headache medications for at least 3 months prior to medication of stable doses of prophylactic headache medications for at least 3 months prior to the initiation of BoNT-A treatment and during the study, it was noticed that headache intensity and frequency decreased in a significant number of the patients with one BoNT-A injection session and concomitant prophylactic medication.

CTTH patients often have an insufficient response to preventative medications, which persuades them misuse and abuse analgesics. This mean that the vicious cycle has to be broken in order to make the medication as effective. As the options are limited for CTTH patients who are already refractory to first- and second-line medications, botulinum toxin injection may help to break these vicious cycles. During this study, headache frequency and intensity and analgesic consumption were decreased significantly, indicating that the cycle had been broken. Nevertheless, it was suggested that one single treatment session could be insufficient to treat this chronic pain syndrome. However, our patients were responsive to the medication for CTTH after one BTX injection session.

There are thought to be several mechanisms that contribute to the development of CTTH. Firstly, chronic neurogenic inflammation may lead to abnormal excitation of the peripheral nociceptive afferent fibres, causing an accumulation of pain-producing metabolites which sustains nociceptive input and lead to central sensitisation. Secondly, enhanced responsiveness of the trigeminal nucleus caudalis neurons may lead to pain signal generation through supraspinal facilitation. Patients may also have decreased pain modulation and there may be a generation of spontaneous central pain. These factors may act individually or in combination to give rise to CTTH [28].

There are various theories explaining the proposed efficacy of BoNT-A in the treatment of headaches. This includes a reduction of muscular hyperactivity through disruption of cholinergic innervation and normalisation of excessive muscle spindle activity. Preclinical *in vitro* and *in vivo* evidence demonstrates that botulinum toxin blocks the secretion of a variety of neurotransmitters such as glutamate, calcitonin gene-related peptide and substance P from nociceptive fibres and down-regulates immediate early gene expression. BoNT-A has also been shown to inhibit central sensitisation

of central trigeminovascular neurons. The toxin blocks peripheral sensitisation directly and central sensitisation indirectly [29-33].

The limitations of this study are that it is open-label analysis that is not placebo-controlled or blinded. Second, only CTTH patients with very refractory headaches were included, which can significantly underestimate the potential results of the therapy in less recalcitrant patients. Third, subjects were permitted to use concomitant headache prophylactic medication. Part of the benefits might, therefore, be due to headache prophylactic medication, rather than BoNT-A efficacy alone. However, we achieved the maximum benefit more than with BTX alone or headache prophylactic medication.

The use of BoNT-A has several advantages over conventional treatment options, such as reduced adverse effects and improved patient compliance. The results of this study suggest that BoNT-A may be considered as a potential treatment for refractory CTTH with concomitant headache prophylactic medication headache. Although this study demonstrates interesting initial results, further methodologically rigorous studies comprising large, long-term, prospective, randomised clinical trials in the field of CTTH are required to clarify the effectiveness in breaking the cycle of CTTH.

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