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BRIEF REPORT

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An open label, randomised, pilot study of botulinum toxin type-A in the treatment of chronic tension-type headache

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Abstract The objective was to assess the effect of botulinum toxin type-A (BTX-A) in treating chronic tension-type headache (CTTH). A single centre, open label, pilot study was carried out at the Headache and Pain Center, Neurology Department, Policlinico San Marco, Bergamo, Italy and the Istituto Ortopedico Galeazzi, Milan, Italy. Sixty consecutive patients meeting accepted criteria for CTTH were randomised into 3 equal groups. Group 1: patients injected in fixed points; Group 2: patients injected using the "follow the pain" approach; and Group 3: as per Group 2 but combined with physiotherapy. Patients were assessed for 4 months using a headache diary, and efficacy was evaluated using a verbal rating scale (VRS), changes in headache frequency and drug intake count. At month 3, all groups showed improvements in VRS, mean headache frequency and mean drug intake, with Group 3 showing the greatest improvements in VRS and drug intake. BTX-A may be a promising therapy for treatment of CTTH using the "follow the pain" approach, especially when combined with adjunctive physiotherapy.

Key words Tension-type headache • Botulinum toxin type-A • Pain • Neuromuscular • Physiotherapy

Introduction

Tension-type headache (TTH) is the most common form of headache, having a lifetime prevalence of up to 30% in the general population [1] and so presents a major burden on healthcare costs. Symptoms can vary in intensity, frequency and duration but include aching, tightness, pressure or constriction.

Despite widespread prevalence, little research has been conducted in the field, and effective treatments are limited as the pathogenesis is not completely known. Increased tension in the pericranial muscles may be associated with TTH in some patients [2–4], but the pathophysiological role of this finding is unclear, although possible mechanisms include peripheral, central medullary and central cortical involvement. Hypothetically, increased muscle tension may cause muscular ischaemia leading to the local release of pain-producing substances, and as such, muscle spasm relief may result in pain reduction [5, 6].

Botulinum toxin type-A (BTX-A) acts by binding to the presynaptic nerve terminal where it then becomes internalised and interferes with acetylcholine exocytosis at the neuromuscular junction, thereby inhibiting muscle

contraction, resulting in temporary muscle paralysis. It has been used to treat a variety of central nervous disorders that have an influence on muscular function and are characterised by increased muscle tone and pain, including cranio-cervical dystonia and myofascial pain syndrome. In addition to the motor effects, BTX-A treatment has been shown to have a positive effect on pain, thus indicating a central anti-nociceptive action. This may be due to its inhibition of substance P release and reduction in release of nociceptive neuropeptides from either cholinergic neurons or from C or A delta fibres, preventing local sensitisation of nociceptors and reducing pain sensation. As such, some investigators have suggested that it may have a role in relieving chronic pain associated with TTH [7]. Indeed, early cosmetic use of BTX and some case studies have found alleviation of tension headaches, as well as improvement in migraine headaches, although a clear scientific basis for this finding has yet to be established [8].

In this study, patients with chronic tension-type headache (CTTH) were studied.

Materials and methods

Sixty patients selected under the International Headache Society (IHS) criteria (see Table 1) for CTTH were randomised into 3 groups of 20 patients (28 males, 32 females). Although the IHS classification allows further subdivision of chronic or episodic tension headache into those with and without associated pericranial muscle tenderness, the methods to record this are controversial and as such we did not make this differentiation in this pilot study. All patients gave voluntary written informed consent prior to commencement of any study procedures and the study was approved by the hospital ethics committee. All 3 groups were comparable in terms of age and sex criteria (Group 1: 9 males, 11 females; Group 2: 10 males, 10 females; Group 3: 9 males, 11 females). Mean drug intake prior to receiving BTX-A treatment was recorded for each group (Group 1: 14.5; Group 2: 18.1 and Group 3: 16.35). The groups were comparable in terms of the mean frequency of headaches experienced per month pre-BTX-A treatment (Group 1: 22.75; Group 2: 22.35 and Group 3: 21.2) (see Table 2). Patients with medication overuse were not included in the study.

Table 1 International Headache Society (IHS) criteria for CTTH

Frequency	Daily or near daily
Duration	Constant
Quality	Pressure or band-like
Intensity	Mild to moderate
Location	Bifrontal, holocranial
Associated symptoms	None
Triggers	Stress
Gender distribution	Female≥male
Age at onset	Teens to 30s

From [24]

All patients received BTX-A (Botox®, Allergan Inc) of between 80 and 150 U, with 10 U injected at each site. Group 1 patients were injected at fixed points; Group 2 patients were injected using a "follow the pain" approach where the injection points were selected by agreement between patient indication and examiner's identification of trigger points, based on algometry (the main sites being in the frontal, temporal and occipital areas); and Group 3 used the same technique as for Group 2 but followed by a strict stretching exercise programme specifically developed for injected facial muscle. These exercises comprised stretching the triangolaris, occipitalis, masseter, frontalis and temporalis facial muscles for 5 min five times a day, for a period of 5 weeks.

Patients were assessed over a 4-month period using a headache diary and efficacy was assessed using a 5-point verbal rating scale (VRS) (headache rated as slight, unpleasant, distressing, horrible, dreadful), change in frequency of headache and drug intake count, specifically focusing on the intake of analgesic compounds. An improvement in VRS was defined as a reduction in score of one or more grades following treatment and an improvement in headache frequency and drug intake was defined as a reduction of 25% or more. Statistical analysis was carried out using a one-way ANOVA for the summary of change from pre- to post-treatment and tests of proportions were used to evaluate the improvements within each group.

Results

At month 3, 45% (9/20) of patients in Group 1 (injected at fixed points) showed an improvement using VRS, 65% of

Table 2 Demographic data per group

	Group 1	Group 2	Group 3
Males, n	9	10	9
Females, n	11	10	11
Mean drug intake pre-BTX-A (range)	14.5 (6–24)	18.1 (10–28)	16.35 (8–24)
Mean drug intake post-BTX-A (range)	11.35 (5–16)	13.5 (7–20)	11.45 (6–18)
Mean monthly frequency of headaches pre-BTX-A (range)	22.75 (17–28)	22.35 (16–28)	21.2 (16–28)
Mean monthly frequency of headaches post-BTX-A (range)	17.9 (11–26)	20.25 (11–28)	20.95 (15–28)

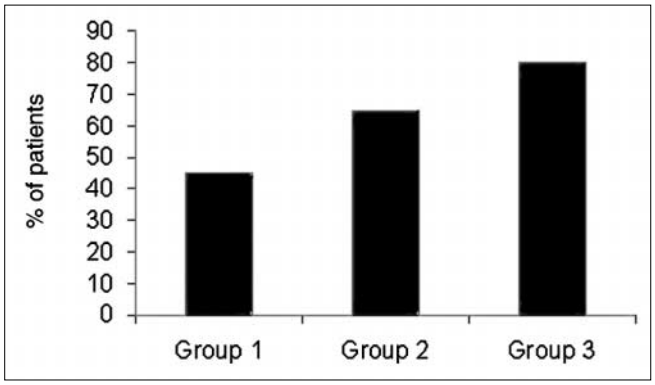

Fig. 1 Overall improvement rates per treatment group at month 3

Group 2 patients ("follow the pain" approach) showed an improvement (13/20 patients) and 80% (16/20) of patients in Group 3 ("follow the pain" approach plus exercise programme) showed improvement (Fig. 1). With respect to mean frequency of headaches (number per month), all groups showed improvements. Group 1 saw the largest improvement in headache frequency (80.0% improved) compared to 60% in Group 2 and 40% in Group 3 (Table 2). This difference between groups was statistically significant (p=0.0064), with the greatest difference between Groups 1 and 3 (p=0.006).

The drug intake counts showed a decreased requirement for analgesic compounds (including NSAIDs) in 45% of patients in Group 1, 70% of patients in Group 2 and 75% of patients in Group 3 (Table 2). The differences between groups though, did not quite reach statistical significance (p=0.0965).

Discussion

Current prophylactic treatments for CTTH are unsatisfactory due to lack of efficacy, intolerable side effects, tachyphylaxis and drug interactions. However, in the search for a well-tolerated treatment, BTX-A is emerging as a promising agent for treatment of headache in patients where the condition is poorly controlled [7].

A number of double-blind and open-label trials have been performed in both migraine and CTTH, many of which demonstrate that BTX-A reduces the frequency and severity of headaches, improves disability scales, improves quality of life and reduces analgesia use [7, 9]. In addition, cost benefits have been shown following BTX-A use, with significant reductions in both analgesic use and expenditure [10].

With respect to migraine, Silberstein et al. [11] conducted a double-blind, placebo-controlled study evaluating migraine patients. There was a significant reduction in moderate-severe migraines, reduction in migraine severity, decrease in migraine frequency, decreased vomiting-associated headache and decrease in use of acute medication for those patients treated with 25 U BTX-A compared to placebo. However, a significantly higher incidence of adverse events occurred in the 75U BTX-A group compared to placebo. Similar positive findings were shown in a study by Klapper et al. [12] who performed a double-blind, placebo-controlled study in 19 migraine patients and results demonstrated reduced duration of pain, as well as a reduction in the frequency of migraines categorised as moderate or severe intensity.

With respect to CTTH, Schmitt et al. [13] performed a double-blind, placebo-controlled, randomised study in which BTX-A injections conferred a slight benefit to patients with CTTH for affective variables at the first month as determined by the West Haven-Yale multidimensional pain inventory (WHYMPI). However, pain reduction, analgesia intake and activity level did not differ between BTX-A and control groups. In addition, this study demonstrated a significant placebo response, which may suggest psychological factors could play a role in this condition. Schmitt et al. suggest individualised patient therapeutic regimens with repeated injections may provide most benefit [13].

A double-blind, placebo-controlled study by Smuts et al. comprising 37 patients with CTTH found a statistically significant improvement of headache symptoms including a decreased pain score in BTX-A treated patients compared to pre-treatment [14]. Similarly, Relja and Klepac [15] performed an open-label study using 40–90 U BTX-A in CTTH patients who were non-responsive to standard therapy. A constant improvement was noted in the number of headache-free days to study conclusion at 18 months.

Positive outcomes were also reported in studies by Schulte-Mattler (open label, pilot study in TTH) who demonstrated the mean area under the curve (AUC) after therapy was significantly lower compared to mean AUC before therapy and a reduced number of headache days occurred post-therapy [16]. Smuts and Barnard (retrospective study in CTTH) [17] and Carruthers et al. (retrospective analysis in TTH) [18] also showed positive results for use of BTX-A, and Relja and Korsic [19] reported a significant, enduring decrease in headache intensity in 16 CTTH patients in a double-blind, placebo-controlled study.

Conversely, other studies have failed to show any significant benefit in the use of BTX-A for treatment of CTTH. Rollnik et al. performed a double-blind, placebo-controlled study with tension-type headache patients but did not find any difference between groups concerning either headache frequency or analgesia consumption [20]. Indeed, one measurement tool, the Everyday-life questionnaire, found a significantly greater improvement for placebo over BTX-A treated patients during follow-up. Another

small pilot study by Rollnik et al. [21] found no demonstrable benefit for use of BTX-A in CTTH, however these negative results may reflect the complexity of chronic headache, with muscle tension being just one contributing factor. These negative results were in agreement with the findings of Zwart et al. [22] who performed an open-label study in 6 CTTH patients which showed no significant difference between treatments regarding pain intensity and evaluation of pressure pain threshold measurements, thus concluding that muscle tension plays only a minor role in CTTH, but further studies to completely exclude the role of muscular tension in pain production were recommended.

The results of this study investigating the effect of different treatment options for the management of CTTH demonstrated that, at month 3, all 3 groups treated showed an improvement in headache, with Group 3 patients ("follow the pain" approach plus physiotherapy) showing the greatest improvement in VRS (80%) and drug intake (75%), although not in the actual frequency of headaches, where a statistically significant greater improvement was seen in Group 1. It can be hypothesised from these findings that BTX-A treatment using the "follow the pain" approach can thus reduce the severity of headaches (and so the need for analgesics) compared to the "fixed point" approach, whereas the "fixed point" approach can reduce the frequency of headaches but with a lesser effect on severity.

However, it must be stressed that the study design did not consider a fourth group of patients infiltrated on the basis of fixed points plus adjunctive physiotherapy.

The effective combination of BTX-A with physiotherapy has previously been demonstrated in the treatment of myofascial pain and dystonia and this approach may reflect the effect of BTX-A on proprioception and muscle memory. Wheeler found in a series of 4 case studies comprising patients with intractable daily headaches, associated muscle tenderness and increased muscle tone that therapeutic benefit resulted when BTX-A treatment was combined with physiotherapy [23] and as such this method warrants further exploration.

In conclusion, these results demonstrate that intramuscular BTX-A injections are a safe, effective, well-tolerated, minimally invasive treatment, with only minor, transient adverse effects. By using the "follow the pain" approach plus adjunctive physiotherapy, this combination treatment may be considered promising for patients with CTTH. This preliminary pilot study demonstrates interesting results but further methodologically rigorous studies comprising large, prospective, randomised clinical trials are required to establish the potential role of BTX-A in the treatment of CTTH. In such studies further subdivision of patients into those with pericranial muscle tenderness and those without would be of interest.

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