Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial

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Abstract
Aim: To investigate the efficacy, safety and tolerability of intradermal and/or submucosal administration of botulinum toxin type A (BTX-A) for patients with trigeminal neuralgia (TN).
Methods: In this randomized, double-blind, placebo-controlled study, 42 TN patients were randomly allocated into two groups, namely, intradermal and/or submucosal injection of BTX-A (75 U/1.5 mL; n = 22) or saline (1.5 mL; n = 20) in the skin and/or mucosa where pain was experienced. The primary endpoints were pain severity (assessed by the visual analogue scale) and pain attack frequency per day. The secondary endpoint was patient's overall response to treatment, assessed using the Patient Global Impression of Change scale. Patients with ≥ 50% reduction in mean pain score at week 12 were defined as responders.
Results: A total of 40 patients completed the study. BTX-A significantly reduced pain intensity at week 2 and pain attack frequency at week 1. The efficacy was maintained throughout the course of the study. More BTX-A treated patients reported that pain had improved by the end of the study. Significantly more responders were present in the BTX-A group (68.18%) than in the placebo group (15.00%). BTX-A was well tolerated, with few treatment-related adverse events.
Conclusions: BTX-A may be an efficient, safe and novel strategy for TN treatment.

Keywords
Botulinum toxin type A, trigeminal neuralgia, double-blind, placebo-controlled, acute treatment

Introduction
Trigeminal neuralgia (TN) is defined as sudden, usually unilateral, severe, brief, stabbing recurrent episodes of pain within the distribution of one or more branches of the trigeminal nerve. This neuropathic disorder has been shown to be profoundly distressing and to negatively impact the patient’s well-being. According to epidemiological studies, approximately 4–28.9/100,000 persons worldwide experience TN (1–3)].
OnabotulinumtoxinA is one of the serotypes (A, B, C1, C2, D, E, F and G) of botulinum neurotoxins derived from Clostridium botulinum (4). It is reported to be effective in the treatment of chronic migraine (5,6) and may be a promising path in headache treatment (7).

The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK and the US Food and Drugs Administration (FDA) approved Botox® (Allergan, Inc., CA, USA) for prophylaxis of headaches in adults with chronic migraine.
In a report that opened up new possibilities for the use of botulinum neurotoxins, Micheli et al. (8) reported the successful treatment of a patient with hemifacial spasm associated with TN with onabotulinumtoxinA. Twitching and pain were both relieved. After this...
report, several other experimental studies have examined the preventive effects of onabotulinumtoxinA in patients with TN. The results of these open-label trials have suggested that onabotulinumtoxinA may be effective in the management of TN (9–14).

To further advance these findings, we conducted a randomized, double-blind, placebo-controlled trial to clarify the efficacy, safety and tolerability of intradermal and/or submucosal administration of botulinum toxin type A (BTX-A) in patients with TN.

Methods

Study design

This was a randomized, double-blind, placebo-controlled and parallel-group clinical study of BTX-A in the management of patients with TN. The overall duration of the study for each patient was 13 weeks, including a 1-week observation period to establish baseline pain symptoms, followed by a 12-week placebo run-in period. Follow-up visits were conducted every week after the injection. Patients were free to discontinue the trial at any time during the double-blind period.

The trial was approved by the local ethics committee. The goal, procedure and safety aspects of the study were explained to each of the patients, and they were informed of the possibility of transient attendant risk of weakness and disfigurement produced by localized administration of BTX-A. Informed consent was included in the documents of each patient.

Eligible patients were randomized in a blinded fashion (1:1) to receive BTX-A (75 U/1.5 mL) or sterile isotonic saline (1.5 mL) in the dermatome and/or mucosa (if the oral mucosa was involved) where pain was experienced.

In addition, after treatments, the patients were asked to guess the medicine injected. Possible answers were ‘BTX-A’, ‘placebo’ or ‘unknown’.

Study participants

Each patient underwent magnetic resonance imaging (39 patients) or computed tomography (three patients) to rule out the presence of structural pathology. According to the current version of the International Classification of Headache Disorders (ICHD-2) (15), all patients were diagnosed with classical TN.

At baseline, patients were usually receiving medications (e.g. carbamazepine, gabapentin, or opioids) to alleviate their pain. These medications were to remain unchanged during the course of the study. No new analgesic therapies were to be initiated at any time during the baseline or placebo run-in period.

Criteria for entry into the study were failure of recent treatment for TN at baseline (pain intensity mean score ≥ 4; mean attack frequency ≥ 4 per day) and understanding the information given relative to the trial, particularly with regard to possible complications such as transient facial weakness.

Exclusion criteria included any medical condition or use of any agent that might put patients at increased risk if exposed to BTX-A (e.g. neuromuscular disorder or agents that might interfere with neuromuscular function), or if they had an infection or skin problem at any of the injection sites. Women of childbearing potential must have a negative pregnancy test result prior to injection. Furthermore, women who were pregnant, nursing, or planning a pregnancy during the study, or who were unable or unwilling to use a reliable form of contraception during the study were also excluded.

Patients who continued to meet all inclusion/exclusion criteria at the end of the baseline phase were randomized and proceeded to the double-blind period.

Treatments

All of the treatment was administered in the treatment room at the Department of Neurology, The First Affiliated Hospital of Zhengzhou University, which is
equipped with all the necessary facilities in case of severe reactions or emergencies.

BTX-A (100 U of Clostridium botulinum type A neurotoxin complex, 5 mg gelatin, 25 mg dextran, and 25 mg saccharose) was obtained from Lanzhou Biological Products Institute, China. The content of each vial was diluted in 2 mL saline solution (0.9%) as recommended by the manufacturer. Patients rested in a supine position on a bed during the injections. Then, 75 U (1.5 mL) of BTX-A were applied at 15 points, 5 U (0.1 mL) per point, between the epidermis and dermis of the skin where pain was experienced according to the patient’s description. The injections were conducted submucosally in the oral mucosa if the pain involved the oral mucosa. The same volume of isotonic saline was administered to the placebo group in the same way. The injections were administered intradermally and/or submucosally using a 1 mL syringe with a 0.45 × 16 mm needle. During the procedure, injection in deeper structures such as the muscles was avoided to prevent unwanted effects on the underlying muscles (Figure 1).

Figure 2. Summary of patients’ disposition. Of 67 patients screened, 42 patients were randomized and 40 patients completed the double-blind phase of this study.

Table 1. Baseline demographics and characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BTX-A (n = 22)</th>
<th>Placebo (n = 20)</th>
<th>Total (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>Mean (SD)</td>
<td>59.14 (12.58)</td>
<td>58.00 (16.91)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Min/max</td>
<td>31/82</td>
<td>30/88</td>
</tr>
<tr>
<td>Mean months since onset of TN</td>
<td>Mean (SD)</td>
<td>72.05 (78.48)</td>
<td>70.00 (80.03)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>72</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Min/max</td>
<td>6/360</td>
<td>6/320</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>13 (59.09%)</td>
<td>10 (50.00%)</td>
<td>23 (54.76%)</td>
</tr>
<tr>
<td>Pain intensity, VAS</td>
<td>Mean (SD)</td>
<td>7.05 (2.03)</td>
<td>6.88 (2.25)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>Min/max</td>
<td>4/10</td>
<td>4/10</td>
</tr>
<tr>
<td>Frequency of TN attacks per day</td>
<td>Mean (SD)</td>
<td>21.71 (22.68)</td>
<td>20.53 (10.38)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Min/max</td>
<td>4/100</td>
<td>10/45</td>
</tr>
<tr>
<td>Concomitant drugs</td>
<td>Carbamazepine</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Opioids</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Efficacy and safety measures

The primary endpoints were pain severity and pain attack frequency per day. On awakening each morning, patients recorded their pain symptoms, including provoking factors, frequency of TN attacks, and severity of pain (according to an 11-point visual analogue scale, VAS) experienced during the previous 24 hours. During the baseline phase, patient demographics, gender, age, presence of trigger zone, side of involvement, and nerve branch involved were also recorded.

The secondary endpoint was the overall response to treatment as assessed on the basis of the Patient Global Impression of Change (PGIC) scale. The PGIC is a self-evaluation of the patient’s overall change since the start of the study according to a seven-point scale (1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; 7, very much worse).

The proportion of responders, defined as patients with $\geq 50\%$ reduction in mean pain score from baseline to endpoint, was also used to assess the efficacy of the treatment.

Safety was measured as the occurrence of adverse events and recorded and documented with information regarding the date of onset, severity, duration, frequency, relationship to study treatment, treatment required (if any), and outcome.

Statistical analysis

All analyses were performed on the intent-to-treat population and all statistical testing was two-sided. The quantitative data was assessed using the mean and standard deviation. The Wilcoxon rank sum test was performed to compare the age, duration of diseases, pain intensity, and frequency of TN attacks per day between BTX-A and placebo. Fisher’s exact test was performed to assess the differences of the gender, PGIC distribution, and the proportion of responders between the two groups. The SPSS 13.0 software package was used for statistical evaluation; $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

The recruitment period was between November 2010 and April 2011, with a 12-week follow-up period after the last patient was enrolled. A total of 67 patients were screened, and 42 were randomized and received BTX-A ($n = 22$) or isotonic saline ($n = 20$). In the end, 40 patients completed the study (Figure 2). There were no significant between-group differences for the majority of important characteristics at baseline (Table 1).

Twenty-eight patients (66.67%) chose ‘unknown’ and five patients (11.90%) guessed the wrong answer.
Only seven patients (16.67%) could guess correctly the assigned medicine injected. Thus, the blinding procedure was successful.

**Efficacy results**

BTX-A significantly reduced the mean VAS scores at as early as week 2 compared to placebo. The effect was sustained throughout the course of the study (Figure 3).

There were no significant differences at week 1 between groups despite a reduction in VAS scores.

Attack frequency was calculated as the number of attacks per day. At endpoint BTX-A was significantly superior to placebo in reducing attack frequency. This effect was evident at as early as week 1, and was sustained throughout the course of the study (Figure 4).

Evaluation of the PGIC demonstrated that 17/22 (77.27%) of the patients who received BTX-A reported improved attack frequency per day.

![Figure 4. Mean attack frequency per day.](image)

![Figure 5. Patient Global Impression of Change (PGIC) results.](image)
that their pain symptoms were 'much improved' or 'very much improved' versus 4/20 (20.00%) of the placebo-assigned patients ($p < 0.01$) (Figure 5).

Response to treatment was defined as a $\geq 50\%$ decrease in pain score from baseline to endpoint, a benchmark typically used in pain trials. Based on this criterion, a higher percentage of BTX-A treated patients 15/22 (68.18%) responded to the treatment compared to as few as 3/20 (15.00%) of the placebo-assigned patients ($p < 0.01$).

**Safety and tolerability**

In the BTX-A group, five patients experienced short-term facial asymmetry on the injection area during dynamic movement. Transient oedema on the area of injection was observed in three patients (two in the BTX-A group, one in the placebo group). Facial asymmetry disappeared within 7 weeks. The facial oedema, which developed within 2 days, disappeared within 7 days.

Two patients (one from the BTX-A group and one from the placebo group) discontinued the study owing to a lack of efficacy. One patient from the BTX-A group added a new analgesic (pregabalin) at week 4. This patient had been previously prescribed carbamazepine (900 mg per day); at baseline, her mean VAS scores was 8.2, and at week 3 it was 7.9. One patient from the placebo group underwent gamma knife surgery at week 6. This patient had also been previously prescribed carbamazepine (600 mg per day); at baseline, his mean VAS score was 7.6, and at week 5 was 7.8.

**Discussion**

TN is an excruciatingly painful neuropathic facial disorder. The pathophysiology of TN has been widely debated. So far, the most widely accepted hypothesis is that TN results from specific abnormalities of trigeminal afferent neurons in the trigeminal root or ganglion. Injury renders the axons hyperexcitable, resulting in paroxysmal pain discharges. Surgeons have shown that, in most cases, there is a compression of the nerve at the entry point of the trigeminal nerve into the brainstem, usually caused by vascular structures. Electron microscopy studies on trigeminal nerves in this area have shown evidence of both demyelination and remyelination (16). These partially injured sensory neurons thus become hyperexcitable and exhibit a phenomenon known as 'after discharge'. These after-discharge bursts may be triggered by an external stimulus and extend beyond the duration of the stimulus. They can then also recruit additional neighbouring neurons, leading to a rapid build-up of electrical activity, which results in a paroxysmal explosion of pain.

Patients with TN usually present a clinical treatment challenge. The medical approach is usually used first in an attempt to treat TN non-invasively. However, all the medical approaches have a poor compliance due to requirements for daily dosage administration, intolerable adverse effects, and/or inadequate efficacy (17). For example the effectiveness of carbamazepine decreased from 69% to 31% within 5–16 years (18) and the efficacy of carbamazepine is compromised by its adverse effects (drowsiness, dizziness, constipation and ataxia) (19). Besides non-invasive treatment, all surgical treatments can be termed destructive or ablative, excluding microvascular decompression, which aims to preserve trigeminal nerve function intact. Microvascular decompression has been widely used for treatment of refractory cases, with a reported success rate of 63–94% (20). However, some attendant serious complications (such as cerebrospinal fluid leaks, aseptic meningitis and ipsilateral hearing loss (20)) associated with intracranial surgery limits the application of this technique.

Thus safer, better tolerated, more effective treatment is imperative for TN. OnabotulinumtoxinA has been reported to be effective in other trigeminally mediated headache disorders, such as hemicrania continua (21) and nummular headache (22), but few studies have evaluated its effectiveness on patients with TN. Bohluli et al. (10) treated 15 patients with refractory TN, each receiving 50–100 U onabotulinumtoxinA at each trigger zone. All of them experienced considerable or even sustained pain relief. These findings were confirmed by the studies by Türk et al. (13) and Züniği et al. (14). In both studies, pain attacks were considerably alleviated. In the former, eight TN patients were given 100 U of onabotulinumtoxinA below and under the zygomatic arch at the involved site (13). Züniği et al. injected onabotulinumtoxinA into the subcutaneous tissue in 12 TN patients; the results were satisfactory in 10 of them (14). Nonetheless, some limitations need to be addressed. The most pressing question is whether the lack of a placebo-controlled comparison group may have overestimated the analgesic effect in patients with TN.

In this placebo-controlled trial, patients receiving BTX-A (75 U/1.5 mL) over the area where pain was experienced showed statistically and clinically significant improvement in pain intensity and attack frequency at each follow-up. Results from this study confirm the results obtained in the above-mentioned case reports and open studies. Amongst the more intriguing finding in this study is the fact that BTX-A produced statistically significant improvements in PGIC scores, considered as the ‘gold standard’ of clinically significant change (23).
In previous studies, onabotulinumtoxinA significantly reduced pain intensity and frequency of attacks within a week or even within several hours of injection. In our study, statistically significant reduction of pain intensity was observed 2 weeks after treatment. This difference may be because of the different treatment methods or of the exacerbation of the effects of BTX-A due to the lack of a control group.

Notwithstanding its ability to control pain, the mechanisms by which onabotulinumtoxinA exerts its direct analgesic effects remain uncertain. Several studies have been conducted to explore the mechanism underlying the potential analgesic action of onabotulinumtoxinA. It has been demonstrated that onabotulinumtoxinA can cause selective weakness of painful muscles and disrupt the spasm–pain cycle, providing sustained pain relief (24). Further studies demonstrated significant results regarding pain, which frequently exceeded the improvement of the muscle spasm and did not correspond strictly to the area of neuromuscular effects (9). Furthermore, as muscle power returns to normal, pain relief is still very evident. These results suggest that the analgesic effect attributed to onabotulinumtoxinA is more complex than simple muscular relaxation (25).

Recent studies showed that onabotulinumtoxinA might inhibit peripheral sensitization of nociceptive fibres, thereby reducing central sensitization by inhibiting the release of glutamate and substance P (26). OnabotulinumtoxinA has been associated with the inhibition of formalin-induced release of glutamate from primary afferent terminals (27). In other studies, onabotulinumtoxinA inhibits depolarization-induced release of substance P and CGRP from nerve fibre terminals in the scalp (28). More research is needed to help understand the mechanism of action of onabotulinumtoxinA on pain in general and TN in particular.

In our study, no significant safety concerns were noted. The adverse events observed in patients were consistent with those seen in previous clinical studies and included short-term facial asymmetry and transient facial oedema. Patients generally found this complication tolerable, compared to the TN attacks. The facial asymmetry may be a result of the effect of BTX-A on muscle contraction.

Although this is the largest study involving the administration of onabotulinumtoxinA on patients with TN to date, the sample size was small. A potential shortcoming is that rare or late-appearing adverse events may not have been detected because of their low incidence, considering the 12-week study duration. Because doses of different formulations of onabotulinumtoxinA are not interchangeable, it is not clear whether 75 U of other formulations of onabotulinumtoxinA can exert the same effects. Although we found that 1 U of the onabotulinumtoxinA we used herein corresponds to 1 U of commercially available Botox® (Allergan, Inc.) in the treatment of blepharospasm and hemifacial spasm (29), more studies are needed to evaluate the effective dose of other formulations of onabotulinumtoxinA in the management of TN.

In summary, the results of this 12-week follow-up, randomized, double-blind, placebo-controlled trial were encouraging. The long duration of action (at least 12 weeks) of BTX-A and limited systemic complications associated with its use make BTX-A an attractive pharmacological agent for the non-surgical management of TN. BTX-A injections would offer some distinct advantages over existing therapies with respect to efficacy and safety.

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References


