Introduction

Migraine is a common disorder that can be episodic or chronic. It is estimated that approximately 14.4% of women and 4.5% of men experience migraine in the Taiwanese population.1 Approximately 1.8% of the population also suffers from transformed migraine (TM).2 Patients with TM have a pattern of moderate, non-descript background headache pain with superimposed episodes of migraine in which the frequency of attacks increases until a pattern of daily headache evolves. The diagnosis of TM is based on having more than 15 days of headache per month lasting more than 4 hours per day with a duration of more than 3 months (Silberstein-Lipton criteria).3 Analgesic overuse is associated with an evolution toward TM, although the exact causal relationship is not clear.4 Recurrent disabling migraine induces significant functional limitations and imposes large individual, social, and economic burdens. Thus, the goals of long-term headache treatment are to reduce the frequency, severity, and disability associated with migraine attacks. Therefore, preventive or prophylactic treatment is indicated for TM patients.

Botulinum Toxin Type A in the Prophylactic Treatment of Transformed Migraine in Taiwanese Patients: A Review of 30 Consecutive Cases

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Background: Botulinum toxin type A (BoNT-A) for the treatment of patients with various forms of migraine has been studied, but there is a paucity of data regarding the use of BoNT-A in Asian headache patients. Our study was designed to evaluate the efficacy of BoNT-A in the treatment of transformed migraine (TM) in a population of Taiwanese patients.

Methods: We retrospectively analyzed 30 patients who underwent BoNT-A treatment for TM from July 2003 to May 2004. Of 30 patients, 14 had palpable muscle tenderness (or tender points) in the pericranial region and 16 did not. All patients received injections into the corrugator, procerus, frontalis, and temporalis muscles (a total of 30 U), while a subset of TM patients with tender points (6 of 14 patients) also received injections to additional muscles based on a follow-the-tenderness approach (mean dose, 45 U).

Results: Twenty-seven of the 30 patients (90%) surveyed reported effective relief of their symptoms with BoNT-A treatment (at least a 50% reduction in the number of headache days or in headache intensity). The greatest reduction in headache days per month and headache intensity was found in TM patients with tender points who received a mean dose of 45 U compared to those who received fixed-site dosing of 30 U.

Conclusion: Our results suggest that BoNT-A may be an effective prophylactic treatment for TM in Taiwanese patients. Interestingly, similar efficacy was demonstrated in TM patients with tender points compared to those without tender points when an additional dose of BoNT-A was injected into the tender muscles in the former. [J Chin Med Assoc 2007; 70(12):535–540]

Key Words: botulinum, fixed site, migraine, muscle tenderness
Chronic pain relief has been achieved with intra-muscular injections of BOTOX® (botulinum toxin type A [BoNT-A]; Allergan Inc., Irvine, CA, USA) for the treatment of primary and secondary cervical dystonia as well as spasticity.5–7 In reviewing the patient selection criteria, inclusion and exclusion criteria, the number of baseline migraine headaches per month and the outcome measures used, there is a wide range of patients treated.8–10 Furthermore, there have been differences in the dosage of BoNT-A used, the location of the injection sites in the face, scalp and neck regions, and whether the assessment of the primary outcome variable was determined after 1 or more treatment sessions. Two widely advocated injection site methods have been utilized. Blumenfeld8 identified BoNT-A injection sites based on the finding of local tenderness on muscle palpation. This is a common practice in the evaluation of patients with cervical dystonia who are to receive BoNT-A.6 Muscle tenderness could represent localized muscle contraction or a symptom of muscle allodynia.11

In this study, we analyzed the use of BoNT-A to treat TM either by injections into the scalp and facial regions only or combined with injections to sites (determined by muscle tenderness) in the neck and shoulder muscles. The aims of this study were to establish dosing, and the choice and number of injection sites required to provide optimal results for Taiwanese patients with TM.

**Methods**

**Patients**

This study included patients who were treated with BoNT-A from July 2003 to May 2004. Subjects considered for participation were the first author’s patients who: (1) met the criteria for TM (Silberstein-Lipton criteria);3 (2) were refractory to oral medication or intolerant of the adverse effects of preventive drugs; and (3) were without secondary causes for headache. We reviewed the records of 32 patients with TM from patients seen in our regional teaching hospital-based Headache Clinic. Two patients were lost to follow-up and were not included in any data analysis. Thirty consecutive patients, aged 25–75 years, with complete records and who satisfied the inclusion criteria were recruited. Patients were injected with BoNT-A for only 1 session and follow-up for 3 months. Exclusion criteria were planned or actual pregnancy, lactation, known allergy or sensitivity to the study medication or its components, and prior injection of anesthetic or steroid into the muscles to be injected in the month prior to study entry.

**Injection method**

The total dose of BoNT-A to be administered was determined by the number of injection sites. After placing the patient in a sitting position, patients were questioned on the anatomic location of the headache. The frontalis, temporalis, and posterolateral neck and shoulder regions were palpated by the first author to identify areas of muscle tenderness, which were identified as tender points (TPs) in this study. Intramuscular injections using sterile technique were administered using 1-mL tuberculin syringes with 30-gauge needles. BoNT-A 100 U vial was reconstituted with preservative-free 0.9% saline to yield 2.5 U/0.1 mL. All patients received injections into the procerus (5 U, 1 site), corrugator (2.5 U each, 2 sides), frontalis (2.5 U each, 2 sites on each side), and anterior and pre-auricular temporalis (2.5 U each, 2 sites on each side) for a total dose of 30 U. If there were TPs on the palpated muscles, some of these patients were randomized to receive injections into the tender muscles. We designed the method for the injection sites of tender muscles and dose of BoNT-A according to Blumenfeld et al12: occipitalis (5 U), trapezius (5–10 U, divided into 2–3 sites), sternocleidomastoid (5–10 U, divided into 2–3 sites), scalene (5–10 U), levator scapulae (5–10 U), semispinalis (5 U, divided into 2 sites) or splenius capitis (5–10 U, divided into 1–3 sites) muscles.

**Outcome measures**

The outcome measures were reduction in headache frequency and intensity, and the data were collected and recorded at baseline and at each clinic visit. At baseline, patients reported headache frequency and intensity in headache diaries, starting 1 month before BoNT-A injection; thus, the baseline data were also the pre-injection data. The patients’ headache diaries were post-injection data after BoNT-A treatment. In order to be included in the study analysis, chart notes had to document headache frequency data and headache intensity data for both the baseline and post-injection visits. Headache intensity was recorded using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). At post-injection visits, patients were asked to assess their symptoms compared with those at baseline, and treatment was reported as being effective if there was at least a 50% reduction in the number of headache days or in headache intensity. Only data from patients’ baseline visit and post-injection visit were analyzed based on the headache diaries. All data included in this study were collected during a 3-month period. Data from visits after 3 months and missing data were excluded from the analysis.
Statistical analysis
Analyses of efficacy parameters were performed using paired-sampled statistics, analysis of variance, and $\chi^2$ tests. Baseline and post-injection scores for headache days, headache intensity and patients’ subjective reports were evaluated for month 1, 2 and 3 post-injection. The efficacy parameter was reduction of headache days per month and headache intensity in month 3 compared with the baseline month. The significance level was set at $p<0.05$.

Results
Thirty patients with TM were recruited in this study, which was 3% of the total number of headache patients under the care of our Headache Clinic during this time period. The mean age of the 30 patients in this study was $51.7\pm13.2$ years (range, 25–75 years); 20 patients (67%) were women. Eighty percent of patients had medication overuse (24 of 30). Overall, the mean BoNT-A dose was $33$ U (range, $30–65$ U). Mean body mass index was $25.5$ kg/m$^2$ (range, $17.9–44.1$ kg/m$^2$). Twenty-four of 30 patients received fixed-site treatment of $30$ U, and 6 patients received combination treatment (> $30$ U; mean total dose, $45$ U), i.e. additional injection sites in the splenius capitis and/or occipitalis and/or trapezius muscles.

Overall, 27 of the 30 patients (90%) surveyed reported effective treatment with BoNT-A (at least a 50% reduction in the number of headache days or headache intensity). Eleven patients (37%) were free of headache. A significant reduction in headache frequency was observed (paired $t$ test, $p<0.001$) with a decrease in the number of headache days per month from 27.2 at baseline to 8.1 (70% reduction) in month 3 (Table 1). Headache intensity decreased significantly from $2.3\pm0.6$ points at baseline to $0.8\pm0.7$ points (65% reduction; paired $t$ test, $p<0.001$) (Table 1).

TPs in the splenius capitis and/or occipitalis and/or trapezius muscles were identified in 14 of the 30 patients. We found no significant difference in headache days per month or headache intensity between those with and without TPs at baseline (Table 1). TM patients with TPs were randomized into 2 groups: Group I received $30$ U by the fixed-site approach; Group II received additional injections in a combination paradigm (mean total dose, $45$ U; dose range, $40–55$ U). The number of headache days per month decreased from 27 at baseline to 11.3 days

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
<th>All patients ($n=30$)</th>
<th>TM without TPs ($n=16$)</th>
<th>TM with TPs ($n=14$)</th>
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</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>52</td>
<td>54</td>
<td>50</td>
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<tr>
<td>Gender</td>
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<tr>
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<td>20</td>
<td>10</td>
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<tr>
<td>Male</td>
<td>10</td>
<td>6</td>
<td>4</td>
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<tr>
<td>HA intensity, baseline</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>2</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Mild to moderate</td>
<td>4</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Moderate</td>
<td>8</td>
<td>6</td>
<td>2</td>
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<tr>
<td>Moderate to severe</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>11</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Mean</td>
<td>2.3</td>
<td>2.3</td>
<td>2.2</td>
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<td>HA intensity, post-injection</td>
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<td>0.8</td>
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<tr>
<td>HA days per month, baseline</td>
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<td>27.3</td>
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<tr>
<td>HA days per month, post-injection</td>
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<td>6.9</td>
<td>9.5</td>
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<tr>
<td>Aura</td>
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<tr>
<td>Combined medication</td>
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<td>6</td>
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</table>

HA = headache; TM = transformed migraine; TPs = tender points.
(58% reduction) in Group I (8 of 14 patients), while the number of headache days per month decreased from 27.5 at baseline to 7.2 days (74% reduction) in Group II (6 of 14 patients) (Figure 1). Headache intensity decreased from 1.9 at baseline to 0.9 (53% reduction) in Group I, while headache intensity decreased from 2.8 at baseline to 0.7 (75% reduction) in Group II (Figure 2).

No systemic reactions or treatment-related adverse events, including blepharoptosis, diplopia, and muscle weakness at the injection sites, were noted in this study.

Discussion

In this study, BoNT-A was shown to be a safe and well-tolerated treatment for TM patients, significantly reducing headache frequency and intensity.

A prospective, double-blind, vehicle-controlled study of 25 U and 75 U BoNT-A treatment in 123 patients with approximately 4 moderate-to-severe migraine attacks per month demonstrated that 25 U of BoNT-A, but not 75 U, resulted in a significant reduction in moderate-to-severe migraine frequency at months 2 and 3 as well as reduction in mean severity at months 1, 2 and 3 ($p<0.05$). In Behmand et al’s study, 24 of 29 patients (83%) with migraine reported a positive response to the injection of a total dose of 50 U BoNT-A. These results prompted us to study the effect of a lower dose of BoNT-A compared to many of the published studies.

In our study, there was no significant difference in headache days per month or headache intensity between TM patients with TPs and those without TPs at baseline. For comparison of the efficacy of the 2 different injection paradigms, TM patients with TPs were randomized into 2 groups: Group I received 30 U by the fixed-site approach and Group II received additional injections in a combination paradigm. Tenderness was only identified in the splenius capitis and/or occipitalis and/or trapezius muscles. The patients who received the combination paradigm seemed to experience a greater reduction in the number of headache days per month and headache intensity compared to those who were treated with the fixed-site approach. However, small case numbers in each group prevented further statistical analysis. Interestingly, there was no significant difference in the reduction of headache days per month and headache intensity between the TM patients who received the combination paradigm and those without TPs, which implies that a larger dose of BoNT-A may be needed in TM patients with TPs to achieve a similar efficacy as in those without TPs.

Blumenfeld et al identified BoNT-A injection sites based on the finding of local tenderness on muscle palpation. This is a common practice in the evaluation and treatment of patients with cervical dystonia who receive BoNT-A. Muscle tenderness can represent the pain of focal muscle contraction or a symptom of allodynia. These TPs from pericranial muscles might act as permanent and powerful triggers of migraine attacks. It is understandable that eliminating them directly might avoid migraine attacks.

Dodick et al observed that in some patients, muscle function returned after 3 months, but the effects of the drug on the elimination of the headaches persisted for longer. We made the same observation in our study, but the duration of the effect of BoNT-A could not be calculated exactly due to variable follow-up duration. The duration of effect of BoNT-A for migraine was not studied in the current report. Our study focused on 1-session injection for our TM patients because in some patients, a single treatment might be enough to break the cycle of chronic
Botulinum toxin as effective treatment for migraine

headaches and there would be no need for repeated injections. The cost of BoNT-A was another major issue because patients had to pay for it themselves.

A randomized, placebo-controlled, parallel design study of 200 U BoNT-A treatment in 60 patients with chronic daily headache (CDH) found that the BoNT-A group strongly tended to improve over the entire 12-week period, 33±23 days vs. 24±16 days without headache (p=0.07), but did not meet the a priori significance criteria. The subject global impressions (p<0.05), subject change in headache impression (p<0.005), and investigator global impressions (p<0.001) all improved in the BoNT-A group compared with placebo. But the authors employed only 1 strategy—“follow the pain”—for all patients with CDH, including chronic tension-type headache (CTTH) and chronic migraine (CM), resulting in unsatisfactory benefits and the tendency to improve more in patients with CTTH than those with CM. The authors also noted the potential weaknesses of their study that included non-optimized injection technique and dose. The injection strategy and dose of BoNT-A may be crucial in the efficacy of BoNT-A in the treatment of CDH.

Even though the precise mechanism by which headache is reduced is not known, based on limited in vitro and in vivo data, it is possible that BoNT-A treatment may reduce the local release of nociceptive neuropeptides, and have either direct or indirect effect on central sensitization. In all patients treated in this study, the injection sites included facial and scalp regions in the distribution of the trigeminal nerve, which is believed to be important in the pathogenesis of migraine. The rationale for the use of intradermal and intramuscular BoNT-A injections in these regions relates to a proposed mechanism of action of BoNT-A: that there may be a neuromodulatory effect of afferent inputs to the trigeminal nucleus from the scalp, skin and muscle within the first branch of the trigeminal nerve and cervical dermatomal distribution. It is hypothesized that BoNT-A has its effect not by direct muscle relaxation but by effects on afferent inputs into the trigeminal nucleus.

Our results suggest that BoNT-A might be an effective prophylactic treatment for TM. In treating Taiwanese and possibly other Asian TM patients, we suggest a starting dose of at least 30 U of BOTOX®. If there is significant muscle tenderness in the posterior scalp, neck and shoulder musculature, then consideration can be given to additional sites.

The weaknesses of this study include: (1) no placebo control group; (2) a retrospective design; and (3) small case number. These may limit the interpretation of the results. With respect to dosing of the neck extensor and rotator muscles, caution is advised. Dosing to these muscles should be reduced from the standard doses used in treating cervical dystonia given the risk of inducing weakness, particularly in the extensor neck muscles (splenius capitis and semispinales). Interestingly, Relja and Telarovic have shown that in cervical dystonia, benefit for pain can be achieved at a dose lower than that required to alter posture. Few studies published have examined the role of BoNT-A in TM, and dosing requirements for non-Caucasian patients with migraine should be explored. Further study of dosing and injection technique in the Asian TM patient population appears warranted given our initial results, the theoretical rationale for the use of BoNT-A, and the significant headache-associated disability experienced by these patients.

References


