

# Targeted Peripheral Nerve-directed Onabotulinumtoxin A Injection for Effective Long-term Therapy for Migraine Headache

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**Background:** Onabotulinumtoxin A (BOTOX) is an FDA-approved treatment for chronic migraine headaches (MHs) that involves on-label, high-dose administration across 31 anatomic sites. Anatomically specific peripheral nerve trigger sites have been identified that contribute to MH pathogenesis and are amenable to both BOTOX injection and surgical decompression. These sites do not always correlate with the on-label FDA-approved injection pattern, but represent a more targeted approach. The efficacy of peripheral nerve-directed BOTOX injection as an independent long-term therapeutic option has not been investigated.

**Methods:** The technique for peripheral nerve-directed therapeutic long-term BOTOX injection is described. A retrospective review was subsequently completed for 223 patients with MH. Sixty-six patients elected to proceed with diagnostic BOTOX injections. Of these, 24 continued long-term therapeutic BOTOX injections, whereas 42 matriculated to surgery. Outcomes were tracked.

**Results:** Initial outcomes included significant improvement in migraine headache index (MHI) ( $53.5 \pm 83.0$ ,  $P < 0.006$ ), headache days/mo ( $9.2 \pm 12.7$ ,  $P < 0.0009$ ), and migraine severity ( $2.6 \pm 2.5$ ,  $P < 0.00008$ ) versus baseline. MHI improved from the initiation of diagnostic injections to the establishment of steady-state injections ( $P < 0.002$ ), and further improved over time ( $P < 0.05$ , mean follow-up 615 days) with no desensitization observed. Decompressive surgery resulted in significant improvement in MHI ( $100.8 \pm 109.7$ ,  $P < 0.0000005$ ), headache days/mo ( $10.8 \pm 12.7$ ,  $P < 0.000002$ ), migraine severity ( $3.0 \pm 3.8$ ,  $P < 0.00001$ ), and migraine duration in hours ( $16.8 \pm 21.6$ ,  $P < 0.0007$ ). MHI improvement with surgery was better than long-term BOTOX injections ( $P < 0.05$ ).

**Conclusions:** Though inferior to surgical decompression, preliminary data demonstrate that targeted peripheral nerve-directed BOTOX injection is an effective primary therapy for MH representing a possible alternative to nondirected BOTOX injection with decreased dosage requirements and potentially decreased cost. (*Plast Reconstr Surg Glob Open* 2017;5:e1270; doi: 10.1097/GOX.0000000000001270; Published online 28 March 2017.)

Migraine headache (MH) is a debilitating neurovascular disorder that affects 35 million Americans annually, with a cumulative lifetime risk for 43% of women and 18% of men.<sup>1,2</sup> In 2010, the U.S. Food and

Drug Administration (FDA) approved BOTOX (onabotulinumtoxin A) for prophylaxis of chronic MH, defined as  $\geq 15$  days/mo with headaches lasting  $\geq 4$  hours/d.<sup>3</sup> Approval was based upon the Phase III REsearch Evaluating

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Migraine Prophylaxis Therapy (PREEMPT) trials demonstrating a decreased frequency of headache days and total cumulative headache hours with BOTOX versus placebo in 2 double-blinded placebo-controlled trials (PREEMPT 1 and 2).<sup>4-6</sup> The on-label injection pattern includes the broad administration of 155 units of BOTOX across 31 sites representing 7 head and neck muscle groups, including the corrugators, procerus, frontalis, temporalis, occipitalis, cervical paraspinal, and trapezius muscle groups<sup>3</sup> (Fig. 1A–C). The PREEMPT trials also included the option to increase the dosage to 195 units across 39 sites with extra administration for the temporalis, occipitalis, and trapezius muscle groups at the clinician’s discretion.

The injection sites used in the PREEMPT trials were not selected with consideration for the evidence that specific anatomic peripheral nerve trigger sites exist that are known to contribute to migraine pathogenesis.<sup>7-18</sup> Rather, these sites represent a “shot-gun” approach to chemodenervation of most major head and neck muscle groups.

In 2000, Guyuron et al.<sup>19</sup> first described the relief of MH in patients undergoing corrugator supercillii resection with cosmetic browlift procedures. Henceforth, the efficacy of surgical decompression of defined peripheral nerve trigger sites such as the supraorbital (SON), supraorbital (STN), zygomaticotemporal (ZTN), greater occipital nerves (GON), lesser occipital nerves, and auriculotemporal nerves has been well established.<sup>19-31</sup> Robust anatomic evidence exists that characterizes the patterns of compression for these peripheral nerve trigger sites.<sup>7-18</sup>

Though constellation of symptoms has been shown to be equally diagnostically effective in experienced hands,<sup>29</sup> many nerve decompression studies have utilized peripheral nerve-directed BOTOX administration to help diagnose patient-specific trigger sites.<sup>32,33</sup> Although Behmand et al.<sup>34</sup> proposed the use of single-site BOTOX injection into the corrugator supercilli muscles for the treatment of MH, the long-term efficacy of targeted, patient-specific, peripheral nerve-directed BOTOX injections as a *primary therapy* for MH has not been evaluated.

## MATERIALS AND METHODS

Between 2005 and 2013, 223 patients presented to the senior author’s practice (J.E.J.) for treatment of MH. After institutional review board approval, data were obtained from a retrospective chart review. All patients were officially diagnosed with MHs by a board-certified neurologist.

Sixty-six patients completed diagnostic BOTOX injections. The remaining patients were lost to follow-up either because of lack of initial response to BOTOX, or more commonly, because of out of pocket expense. At the initial visit, patients identified the origin of their pain and pattern of progression. Patients were then offered targeted peripheral nerve-directed BOTOX injection (Fig. 1D–F) at the site of their migraine initiation. Patients were followed for the effect of BOTOX at this site, and addition-

al trigger sites were addressed in a sequential manner if symptoms remained, per the original protocol published by Guyuron et al.<sup>22</sup> A minimum of 1 month transpired between injections so as to precisely identify the incremental effect of each injection, allowing for identification of an individualized, patient-specific pattern of trigger sites.

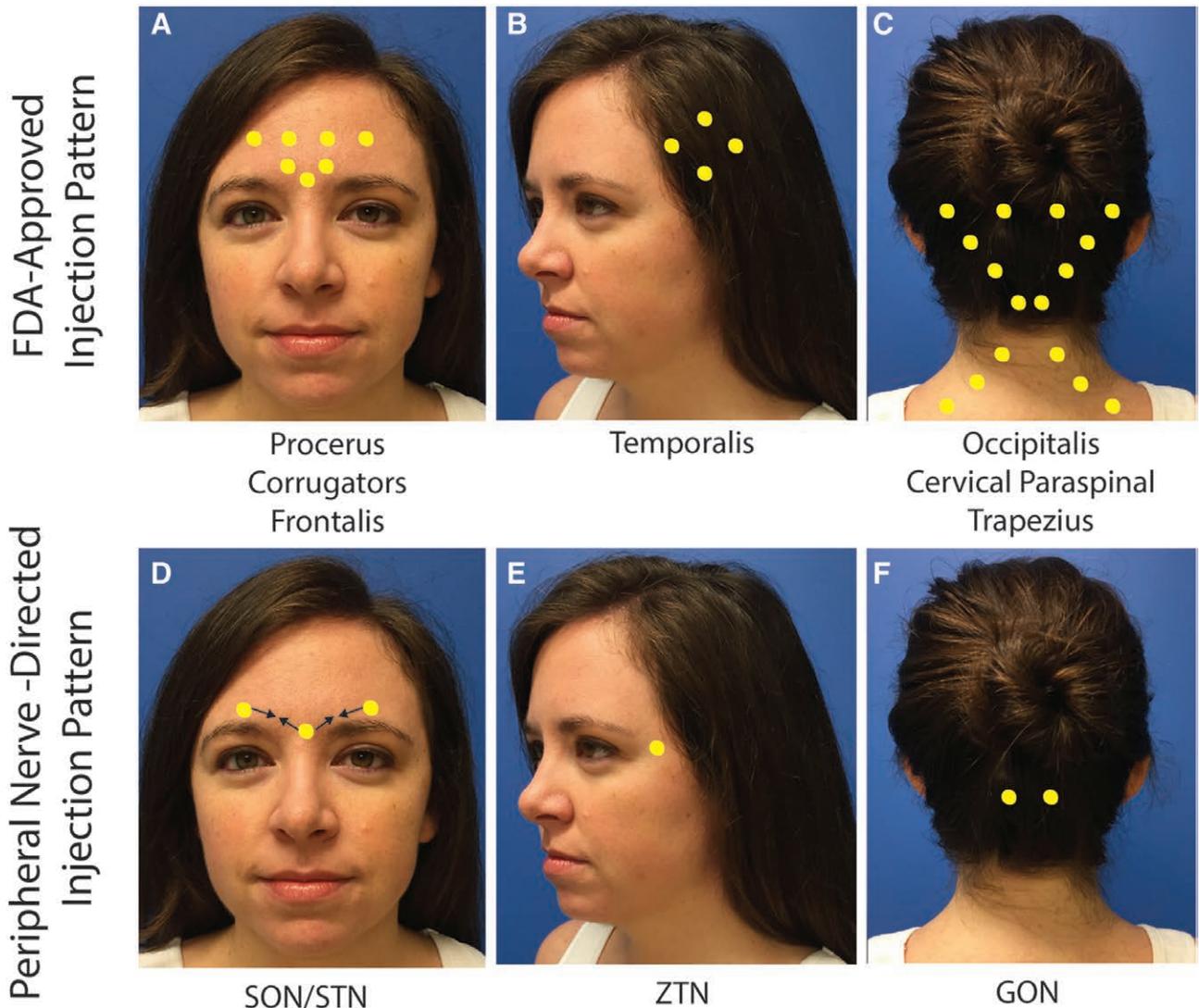
BOTOX was diluted to a concentration of 25 units/ml. Twenty-five units were injected for each GON trigger site (See video, Supplemental Digital Content 1, which shows the targeted BOTOX injection technique for the greater occipital nerve (GON) trigger site. This video is available in the “Related Videos” section of the Full-Text article on PRSGlobalOpen.com or available at <http://links.lww.com/PRSGO/A394>); 12.5 units were injected for each SON/STN trigger site (See Video, Supplemental Digital Content 2, which shows the targeted BOTOX injection technique for the supraorbital and supratrochlear nerve (SON/STN) trigger site. This video is available in the “Related Videos” section of the Full-Text article on PRSGlobalOpen.com or available at <http://links.lww.com/PRSGO/A395>); and 18.75 units were injected for each ZTN trigger site. (See Video, Supplemental Digital Content 3, which shows the targeted BOTOX injection technique for the zygomaticotemporal nerve (ZTN) trigger site. This video is available in the “Related Videos” section of the Full-Text article on PRSGlobalOpen.com or available at <http://links.lww.com/PRSGO/A396>.) There were no changes to pre-existing migraine medication regimens during the diagnostic evaluation to obviate confounding factors.

Of the 66 patients who underwent diagnostic BOTOX injections, 24 continued long-term BOTOX injections, whereas 42 matriculated to surgery. Because positive response to BOTOX was used as a preoperative diagnostic tool, all 66 patients included in this study were offered surgical decompression. The 24 patients who proceeded with long-term BOTOX injections either preferred the minimally invasiveness of the therapy or found surgery cost-prohibitive if denied by insurance. “Long-term BOTOX injections” were defined as repeat injections at the previously identified patient-specific trigger site pattern, and were recommended at 3-month intervals. The surgical decompression techniques of the 4 trigger sites that were utilized in this study have been recently reviewed.<sup>31</sup>

Pretreatment data were collected, including age at presentation and onset, gender, and baseline headache frequency, intensity, and duration. Outcomes were tracked, including migraine headache index (MHI, headache days per month × migraine severity on 1–10 scale × migraine duration in fraction of 24 hours), amount of BOTOX administered, the addressed trigger sites, and complications.

Data were evaluated on an interval basis for patients undergoing long-term BOTOX injection to allow for evaluation of symptom progression over time. A mixed effects regression model was utilized, allowing for correlation and interdependencies resulting from repeated measures on the same subject. Data are reported with *P*-values and error variances. Continuous variables representing pre- and posttreatment data were otherwise evaluated using a paired Student’s *t* test with *P*-values.

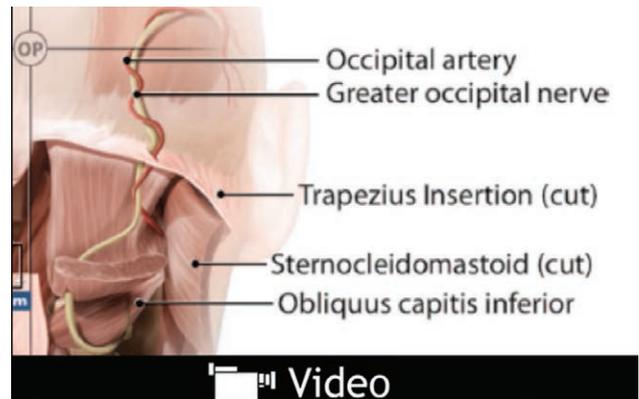
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**Fig. 1.** Current FDA-approved injection pattern versus targeted peripheral nerve-directed injection pattern. The current FDA-approved injection pattern includes chemodenervation of 7 head and neck muscle groups (A–C). The total units of BOTOX injected for each site bilaterally include: corrugators 10U, procerus 5U, frontalis 20U (A), temporalis 40U (B), occipitalis 30U, cervical paraspinal 20U, and trapezius 30U (C). By comparison, peripheral nerve-directed BOTOX injection targets fewer sites with a smaller total quantity of BOTOX (D–F). The total units of BOTOX injected for each site bilaterally include: supraorbital nerve/supratrochlear nerve 25U (D), zygomaticotemporal nerve 37.5U (E), and greater occipital nerve 50U (F).



**Video Graphic 1.** Targeted BOTOX injection technique for the greater occipital nerve (GON) trigger site.



**Video Graphic 2.** Targeted BOTOX injection technique for the supraorbital and supratrochlear nerve (SON/STN) trigger site.



**Video Graphic 3.** Targeted BOTOX injection technique for the zygomaticotemporal nerve (ZTN) trigger site.

## RESULTS

### Pretreatment Patient Characteristics

Patients undergoing long-term BOTOX injections were entirely women with an average age of migraine onset of 23 ( $\pm 14$ ) years, versus those who underwent surgical decompression where 83% were women with an average age of onset of 22 ( $\pm 11$ ) years. The average age of presentation to the senior author’s practice was 46 ( $\pm 12$ ) and 41 ( $\pm 14$ ) years for the Botox and surgery cohorts, respectively. The baseline MHI for the BOTOX group was 74 ( $\pm 82$ ), and for the surgery group was 101 ( $\pm 110$ ). The mean length of follow-up was 615 ( $\pm 448$ ) and 425 ( $\pm 280$ ) days for the BOTOX and surgery cohorts, respectively. Overall, there were no statistically significant differences in the baseline characteristics of the 2 cohorts (Table 1).

### Targeted Peripheral Nerve–directed Botox Injection Is an Effective Long-term Therapy for Migraine Headache

After the initial visit, the time elapsed to complete diagnostic BOTOX injections and reach a “steady-state” of repeated injections at the same trigger sites averaged 5 months ( $149 \pm 125$  days) and ranged from 1 to 3 injection visits. This was dependent on the number of trigger sites identified. Compared with baseline, there was significant sustained improvement with this regimen. Data were analyzed after diagnostic BOTOX injections had been completed and the patient had received 1 series of injections in the pattern of their long-term regimen. At this

time point, average MHI decreased from 73.7 ( $\pm 81.7$ ) to 40.5 ( $\pm 78.0$ ) ( $P < 0.0002$ ). Average headache days/mo decreased from 13.6 ( $\pm 11.2$ ) to 6.2 ( $\pm 4.9$ ) ( $P < 0.002$ ), and average severity decreased from 8.1 ( $\pm 1.5$ ) to 5.8 ( $\pm 2.1$ ) ( $P < 0.0001$ ). Migraine duration was not affected significantly by long-term BOTOX injections.

Long-term follow-up was 615 ( $\pm 448$ ) days for the BOTOX cohort. The average time interval between visits was 85 ( $\pm 65$ ) days and included an average of 6.7 ( $\pm 3.8$ ) injection cycles. At the last follow-up, patients demonstrated continued further improvement from the initiation of their long-term injection regimen. MHI further improved from 40.5 ( $\pm 78.0$ ) to 25.4 ( $\pm 72.0$ ) ( $P < 0.05$ ). Average headache days/mo further improved from 6.2 ( $\pm 4.9$ ) to 4.0 ( $\pm 4.9$ ) ( $P < 0.01$ ). Migraine severity remained stably improved from baseline, but was not significantly different from the initiation of steady-state injections. Migraine duration remained unchanged from baseline (Fig. 2).

Subgroup analysis was performed for patients who experienced  $>15$  MH days/mo versus those who experienced  $<15$  days/mo. For those who experienced  $>15$  MH days/mo ( $n = 8$ , average  $28 \pm 4$  days/mo), significant reductions were seen in headache days/mo from 28.4 ( $\pm 3.9$ ) to 4.0 ( $\pm 2.6$ ) ( $P < 0.000007$ ) and migraine severity from 7.5 ( $\pm 1.6$ ) to 4.9 ( $\pm 2.0$ ) ( $P < 0.01$ ). The change in migraine duration was not significant. However, for those who experienced  $<15$  MH days/mo ( $n = 16$ , average  $6 \pm 3$  days/mo), MHI decreased from 75.2 ( $\pm 84.0$ ) to 23.4 ( $\pm 40.1$ ) ( $P < 0.03$ ), migraine severity decreased from 8.4 ( $\pm 1.4$ ) to 5.8 ( $\pm 2.7$ ) ( $P < 0.002$ ), and migraine duration decreased from 1.4 ( $\pm 1.2$ ) to 0.6 ( $\pm 0.7$ ) ( $P < 0.02$ ). Headache days/mo was the only variable that was not significantly reduced in the “fewer than 15 MH days per month” subgroup (Table 2).

There were several pertinent negative observations within this study. First, there was no desensitization to BOTOX observed over time. We compared patient outcomes, including MHI, MH days/mo, severity, and duration with the total number of units of BOTOX received during the course of therapy. There was no decrease in response in the follow-up time frame that correlated with increasing exposure to BOTOX. Secondly, an attempt was made to define an optimal time interval where patient symptoms were likely to recur without re-administration of BOTOX. However, as the average intervisit time interval in this study was 85 days, there were not enough patients who fell outside of the recommended 3-month interval to define a maximal interval. These data support, however, that an interval of 85 days is effective in using an anatomically directed BOTOX as a primary therapy for MH.

**Table 1. Demographics**

|                             | Long-term Botox<br>(n = 24) | Surgery<br>(n = 42)    | P    |
|-----------------------------|-----------------------------|------------------------|------|
| Female                      | 24 (100%)                   | 35 (83%)               |      |
| Male                        | 0 (0%)                      | 7 (17%)                |      |
| Average age at presentation | 46 years ( $\pm 12$ )       | 41 years ( $\pm 14$ )  | 0.12 |
| Age at onset                | 23 years ( $\pm 14$ )       | 22 years ( $\pm 11$ )  | 0.78 |
| Length of follow-up         | 615 days ( $\pm 448$ )      | 425 days ( $\pm 280$ ) | 0.07 |
| Baseline MHI                | 74 ( $\pm 82$ )             | 101 ( $\pm 110$ )      | 0.09 |

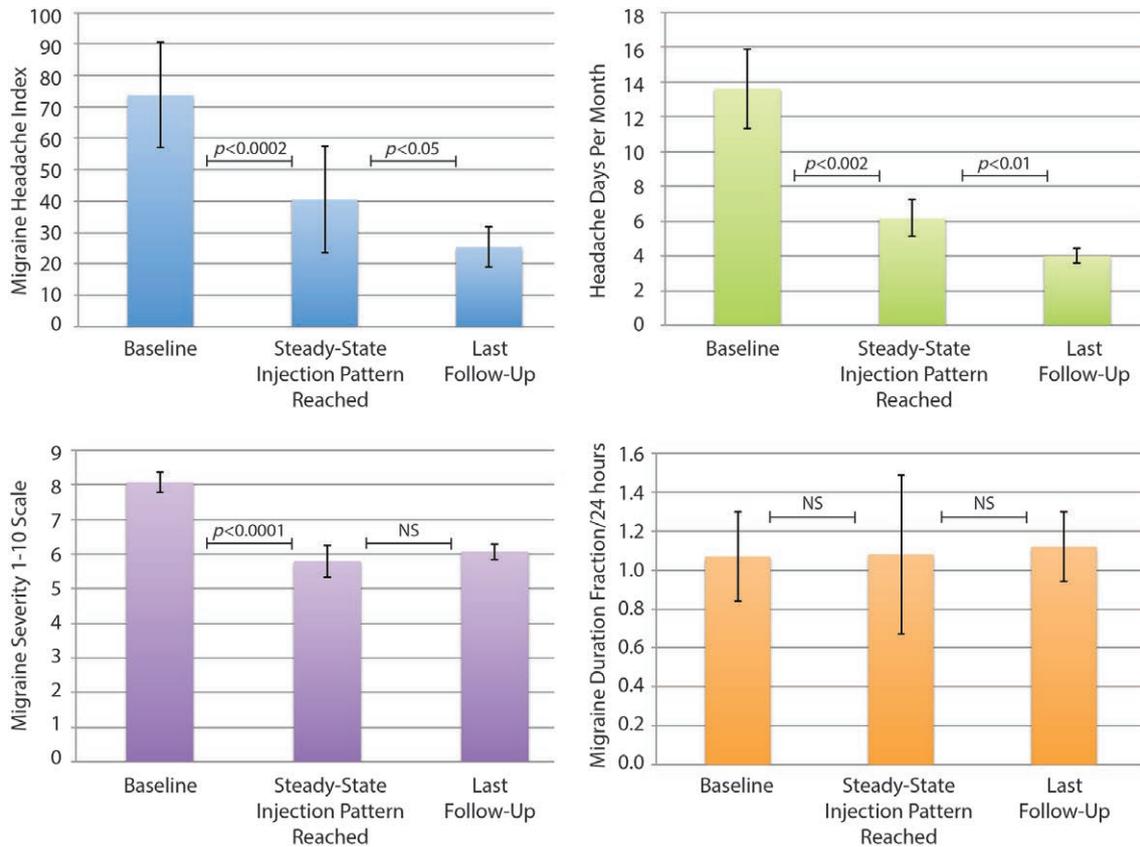
MHI: frequency  $\times$  severity  $\times$  duration.

Data are presented as average  $\pm$  1 standard deviation.

P-values comparing Botox versus Surgery were calculated using 2-tailed Student’s *t* test.

### Targeted Peripheral Nerve–directed Long-term Botox Versus Surgical Decompression

Outcomes at the last available follow-up were compared between those who underwent targeted long-term BOTOX injections versus those who underwent surgery. The trigger sites addressed in the different treatment arms are described in Table 3. Both targeted long-term BOTOX and surgery were effective versus baseline. Specifically, the average improvement of headache days/mo was 9.2 ( $\pm 12.7$ ) ( $P < 0.002$  versus baseline) and 10.8 ( $\pm 12.7$ ) ( $P < 0.000002$  vs baseline)



**Fig. 2.** Peripheral nerve–directed BOTOX improves migraine symptoms over time. Compared with baseline, significant improvement was noted in MHI, headache days per month and migraine severity after patients had reached a steady-state, long-term injection regimen. Interval, further improvement was noted in MHI and headache days per month at the last follow-up visit. MHI: frequency × severity × duration. Frequency: number of migraine days within past month. Severity: migraine severity on 1–10 scale, with 1 = best and 10 = worst. Duration: fraction of 24 hours. A mixed effects regression model was utilized to evaluate these data, presented as ±SEM with *P*-values.

**Table 2. Subgroup Analysis for Patients with More or Fewer than 15 MH Days per Month**

|                                       | ≥15 MH Days/mo (n = 8, Average 28 ± 4 d) | ≤15 MH Days/mo (n = 16, Average 6 ± 3 d) |
|---------------------------------------|--|--|
| Average MHI pretreatment (±SD)        | 70.7 (±82.3)                             | 75.2 (±84.0)                             |
| Average MHI posttreatment (±SD)       | 13.7 (±18.1)                             | 23.4 (±40.1)                             |
| Average improvement (±SD)             | 57.0 (±83.3)                             | 51.7 (±85.5)                             |
| <i>P</i>                              | 0.09                                     | 0.03                                     |
| Average frequency pretreatment (±SD)  | 28.4 (±3.9)                              | 6.2 (±3.3)                               |
| Average frequency posttreatment (±SD) | 4.0 (±2.6)                               | 4.7 (±5.4)                               |
| Average improvement (±SD)             | 24.4 (±5.9)                              | 1.6 (±6.7)                               |
| <i>P</i>                              | 0.000007                                 | NS                                       |
| Average severity pretreatment (±SD)   | 7.5 (±1.6)                               | 8.4 (±1.4)                               |
| Average severity posttreatment (±SD)  | 4.9 (±2.0)                               | 5.8 (±2.7)                               |
| Average improvement (±SD)             | 2.6 (±2.1)                               | 2.6 (±2.8)                               |
| <i>P</i>                              | 0.01                                     | 0.002                                    |
| Average duration pretreatment (±SD)   | 0.3 (±0.4)                               | 1.4 (±1.2)                               |
| Average duration posttreatment (±SD)  | 2.1 (±4.8)                               | 0.6 (±0.7)                               |
| Average improvement (±SD)             | 0  | 0.8 (±1.2)                               |
| <i>P</i>                              | NS                                       | 0.02                                     |

MHI: frequency × severity × duration.

Frequency: number of migraine days within past month.

Severity: migraine severity on 1–10 scale, with 1 = best and 10 = worst.

Duration: fraction of 24 hours.

Data are presented as average ± 1 standard deviation.

*P*-values compare pretreatment versus posttreatment and were calculated using a paired Student’s *t* test.

for long-term BOTOX and surgical decompression, respectively. The average improvement in headache severity was 2.6 (±2.5) (*P* < 0.00004 vs baseline) and 3.0 (±3.8) (*P* < 0.000007 vs baseline) for BOTOX and surgery, respectively. Only sur-

gery demonstrated an average improvement in headache duration with a decrease of 16.8 hours/24 hours (*P* < 0.00002 vs baseline). Overall, MHI improved by 53.5 (±83.0) (*P* < 0.004) for BOTOX and 100.8 (±109.7) (*P* < 0.0000005) for surgery

**Table 3. Trigger Sites by Treatment**

|                                   | Long-term Botox<br>(n = 24) | Units of Botox<br>Per Visit* | Surgery<br>(n = 42) |
|-----------------------------------|-----------------------------|------------------------------|---------------------|
| SON/STN                           | 0 (0.0%)                    | n/a                          | 1 (2.4%)            |
| SON/STN + ZTN                     | 1 (4.2%)                    | 62.5 units                   | 8 (19.0%)           |
| GON                               | 2 (8.3%)                    | 50 units                     | 5 (11.9%)           |
| LON + GON                         | 0 (0.0%)                    | n/a                          | 1 (2.4%)            |
| SON/STN+ GON                      | 1 (4.2%)                    | 81.25 units                  | 0 (0.0%)            |
| SON/STN + ZTN + GON               | 20 (83.3%)                  | 112.5 units                  | 12 (28.6%)          |
| SON/STN + ZTN+ septoplasty        | n/a                         | n/a                          | 4 (9.5%)            |
| SON/STN + ZTN + GON + septoplasty | n/a                         | n/a                          | 12 (28.6%)          |

\*Botox diluted to 25 units/ml.

**Table 4. Long-term Botox Versus Surgery Outcomes**

|                                       | Long-term Botox (n = 24) | Surgery (n = 42) |
|---------------------------------------|--------------------------|------------------|
| Average MHI pretreatment (±SD)        | 73.7 (±81.6)             | 114.2 (±106.9)   |
| Average MHI posttreatment (±SD)       | 20.2 (±34.2)             | 13.4 (±36.1)     |
| Average improvement (±SD)             | 53.5 (±83.0)             | 100.8 (±109.7)   |
| <i>P</i>                              | 0.004                    | 0.000005         |
| Average frequency pretreatment (±SD)  | 13.6 (±11.2)             | 16.0 (±10.5)     |
| Average frequency posttreatment (±SD) | 4.5 (±4.6)               | 5.2 (±8.5)       |
| Average improvement (±SD)             | 9.2 (±12.7)              | 10.8 (±12.7)     |
| <i>P</i>                              | 0.002                    | 0.000002         |
| Average severity pretreatment (±SD)   | 8.1 (±1.5)               | 7.8 (±1.9)       |
| Average severity posttreatment (±SD)  | 5.5 (±2.5)               | 4.9 (±3.6)       |
| Average improvement (±SD)             | 2.6 (±2.5)               | 3.0 (±3.8)       |
| <i>P</i>                              | 0.00004                  | 0.000007         |
| Average duration pretreatment (±SD)   | 1.1 (±1.1)               | 1.05 (±1.05)     |
| Average duration posttreatment (±SD)  | 1.1 (±2.8)               | 0.4 (±0.6)       |
| Average improvement (±SD)             | 0                        | 0.7 (±0.9)       |
| <i>P</i>                              | NS                       | 0.00002          |

MHI: frequency × severity × duration.

Frequency: number of migraine days within past month.

Severity: migraine severity on 1–10 scale, with 1 = best and 10 = worst.

Duration: fraction of 24 hours.

Data are presented as average ± 1 standard deviation.

*P*-values compare pretreatment versus posttreatment and were calculated using a paired Student's *t* test.

(Table 4). The improvement observed in MHI with surgery was statistically significantly better than for long-term BOTOX (*P* < 0.05) (Fig. 3B).

Outcomes were categorized according to percent overall symptom reduction and compared between the long-term BOTOX patients and surgical decompression patients. More patients who underwent surgical decompression experienced either complete elimination of symptoms or >90% reduction of symptoms (21.4% and 45.2% of patients treated with surgery, respectively) compared with long-term BOTOX patients. Although long-term BOTOX is an effective therapy, more of these patients were categorized in a category of >50% reduction of symptoms (41.6% of patients treated with long-term BOTOX) (Fig. 3A).

**Complications after Targeted Long-term Botox Injections and Surgery**

Fifty-five percent of injections overall resulted in a mild adverse outcome on patient survey. Those queried included: development of MH, eyelid/eyebrow ptosis, neck weakness/soreness, weakness with mastication, or diplopia. Headache was the most commonly reported side effect at 24%.

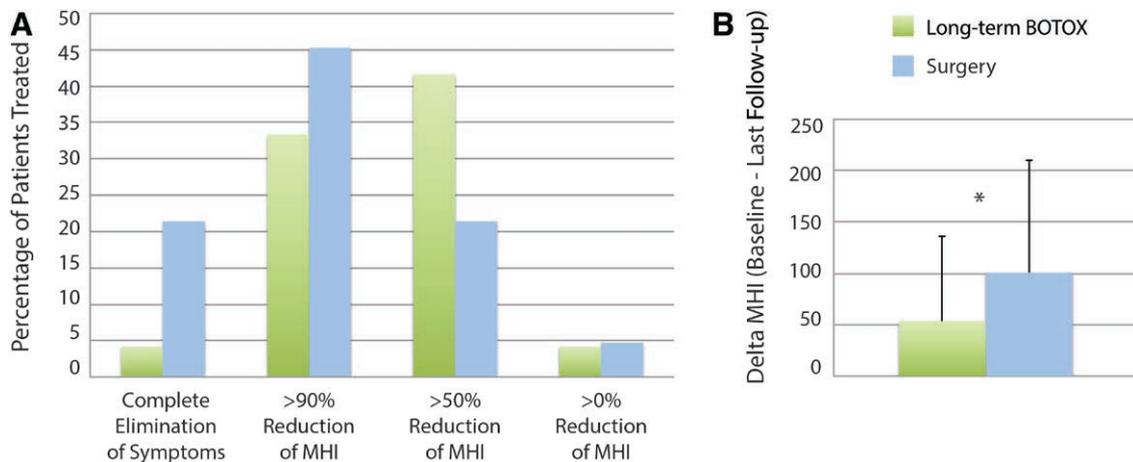
When the SON/STN were injected, mild ptosis occurred 5% of the time and subjective mastication weakness occurred 8% of the time with ZTN injection. No patients

experienced diplopia. When the GON was injected, 12% and 13% resulted in neck self-limited weakness and neck soreness, respectively. No serious adverse outcomes requiring further interventions, hospitalizations, or procedures were reported.

No significant postoperative complications occurred in 42 patients. The most common side effect was temporary numbness at the surgical site or in the targeted nerve distribution in 52% of patients. Transient incisional alopecia occurred in 12% of patients. A minor wound dehiscence occurred in 1 patient and a transient frontal branch facial nerve palsy occurred in 1 patient.

**DISCUSSION**

This study suggests that peripheral nerve-directed BOTOX therapy is an effective long-term therapy for MH. Overall, statistically significant reductions were seen in MHI, headache days/mo, and migraine severity, but not duration. When patients were divided into 2 subgroups, the impact on symptomatology diverged. Specifically, patients who experienced baseline >15 headache days/mo had the greatest effect on reduction of headache days/mo. This is a comparable finding to the original PREEMPT trials. Interestingly, when we evaluated patients who experienced <15 headache days/mo, they did not experience a



**Fig. 3.** Long-term peripheral nerve–directed BOTOX (green) versus surgical decompression (blue) (A, B). Data were derived as the difference between baseline and the last follow-up visit. Differences in MHI were evaluated using Student’s *t* test and are presented as  $\pm 1$  standard deviation. \* $P \leq 0.05$ .

statistically significant decrease in headache days/mo, consistent with prior literature stating that patients with acute, episodic migraine do not derive significant benefit from BOTOX injection. As such, BOTOX is not FDA-approved for acute episodic MH. However, when we applied an expanded definition of patient outcomes, including MHI and its subcategories (standard practice in the migraine surgical literature), we did observe a statistically significant improvement from peripheral nerve–directed BOTOX injections on other parameters. Specifically, migraine severity, duration, and MHI were all significantly improved. Thus, these data not only validate the findings from the PREEMPT trials, but also highlight the benefit of using MHI and its subcategories when evaluating patients. MHI, importantly, takes into account positive outcomes that headache days/mo alone might miss. This is important to consider because insurance approval of BOTOX as a primary therapy is not always guaranteed in our patient population who experience baseline  $<15$  headache days/mo.

The mechanism of migraine prophylaxis with peripheral administration of botulinum toxin is not understood. *Clostridium botulinum* elaborates 7 exotoxins (A–G), all of which are known to interfere with the release of neurotransmitters by interfering with vesicle fusion at the pre-synaptic membrane. Botulinum toxin A, in particular, is a 150-kDa zinc-dependent protease that specifically cleaves synaptosome-associated protein 25 (SNAP-25), preventing vesicle fusion and subsequent neurotransmitter release.<sup>35</sup> This is best defined in the context of the neuromuscular junction, where SNAP-25 cleavage results in the failure of acetylcholine release and subsequent lack of activation of the postsynaptic muscle fibers, resulting in paralysis.

In the context of pain syndromes, the analgesic and antinociceptive effect of botulinum toxin is well established; however, the mechanism is less clear. One hypothesis is that botulinum toxin inhibits the release of neurotransmitters, such as the inflammatory protein calcitonin gene-related peptide, glutamate, or substance P,<sup>36</sup> from primary peripheral nociceptive neurons to the central nervous system, indirectly inhibiting central sensitization. In ad-

dition to the release of neurotransmitters, appropriate vesicle trafficking and fusion is also required for delivery of membrane-bound proteins to the cell surface. Some have suggested that botulinum toxin creates interference with placement of specific surface membrane ion channels required for signal transduction, such as the transient receptor potential channels, within nociceptive neuronal membranes.<sup>37</sup>

The trigeminovascular system is highly implicated in migraine pathogenesis. Peripheral, first-order afferent nociceptive neurons include those derived from both extracranial structures of the face and skull,<sup>37</sup> the intracranial meninges and blood vessels of the head and neck.<sup>36</sup> The greater and lesser occipital nerves also contribute nociceptive afferent input that converges with higher order, downstream trigeminal input.<sup>37</sup> A recent review not only highlights the fact that “Injection of onabotulinumtoxin A at the designated therapeutic sites in the head, neck and shoulder would result in internalization of the neurotoxin into nearby motor or sensory neurons,” but also comments that “It is difficult to explain at the cellular level how injection of onabotulinumtoxin A in the typical pattern used therapeutically to treat chronic migraine could suppress activation of primary and secondary trigeminal nociceptive neurons directly implicated in migraine pathology.”<sup>36</sup>

These considerations raise an important fundamental question about the intended target of BOTOX in migraine therapy. Should the target be peripheral head and neck muscle groups, as is the current FDA-approved regimen? Or should the target be anatomically defined peripheral nerves, which clinical studies evaluating surgical decompression have reproducibly demonstrated exist as trigger sites for MH? Given the differences in trial design, patient inclusion criteria, sample size, and outcome measures, it is difficult to perform a direct head-to-head comparison between the results of this study and those from the PREEMPT trials. However, simplistically speaking, the data presented here demonstrate equivalent, if not superior, reduction in symptoms with less BOTOX. The 2 PREEMPT trials demonstrated an improvement of

1.4 and 2.3 headache days/mo over the effect observed with placebo injection. In a comparable patient population who experienced >15 headache days/mo at baseline, our patients experienced a reduction of 24.4 headache days/mo ( $P < 0.000000004$  vs baseline), though this was a small sample size and was not placebo controlled. Therefore, it is possible that not only the additional injection sites in the current FDA-approved pattern are not only redundant and unnecessary, but also the broad injection pattern hinders the therapeutic effect by reducing the concentration of drug that is ultimately delivered to the effective end-target. Interestingly, a preclinical model has recently demonstrated that higher potency, peripheral application of botulinum toxin to extracranial peripheral nerve branches at suture lines had greater effect than a more diffuse application pattern at both extracranial nerve endings and into local muscle groups.<sup>38</sup> Peripheral nerve-directed injections are achieved with fewer units of BOTOX, though they deliver a more concentrated dose at the intended nerve target, with the benefit of decreased BOTOX exposure for patients and the potential for decreased cost.

This study is not without limitations including its retrospective design and small sample size. Variability was noted in baseline headache characteristics, including the fact that patients with less severe HA chose nonoperative management more frequently, though none of these differences were statistically significant. Although the findings of the subgroup analysis performed in Table 2 are interesting, these observations stem from an even further limited sample size. Further, attrition was significant. The majority of this study occurred either before or shortly after FDA approval of BOTOX for MH and this had a significant impact on insurance coverage of BOTOX, which was variable on a case-by-case basis. In conversation with patients within the senior author's practice, this constituted the largest factor in the attrition process. However, it is also possible that those who did not experience beneficial effect were lost to follow-up, resulting in unavoidable bias within the study design.

## CONCLUSIONS

This work is the first to demonstrate that targeted peripheral nerve-targeted BOTOX injection is an effective long-term therapy for MH. Further, the patients presented in this study have the opportunity to matriculate to the surgical arm for definitive peripheral decompression, which was demonstrated in this study to be superior to long-term BOTOX therapy.

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## PATIENT CONSENT

*Patients provided written consent for the use of their images.*

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