Positive Botulinum Toxin Type A Response Is a Prognosticator for Migraine Surgery Success

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Background: The objective of the study was to determine whether botulinum toxin type A injections can serve as a prognosticator for migraine surgery success.
Methods: Patients who underwent migraine surgery from 2000 to 2010 by the senior author (B.G.) were reviewed. Patients were included if they had botulinum toxin type A injection before surgery; had completed postinjection, postsurgery Migraine Headache Questionnaires; and had at least 1-year follow-up. Outcome variables include patient demographics and Migraine Headache Index. Treatment success was defined as at least a 50 percent reduction in Migraine Headache Index.
Results: One hundred eighty-eight patients were included; 144 reported successful migraine headache reduction after injection (success group) and 44 did not (failure group). The groups were well matched for age, migraine headache characteristics, and number of surgical sites ($p > 0.05$). The surgery success rate was significantly higher in the success group overall (90.3 percent versus 72.3, $p = 0.003$), and in patients who reported botulinum toxin type A success and subsequent same-site surgery (97.9 percent versus 71.4 percent, $p < 0.0001$). Botulinum toxin type A success was prognostic for surgery success at the frontal trigger site (trigger site I) (92.5 percent versus 69.2 percent, $p = 0.012$), the temporal trigger site (trigger site II) (95.5 percent versus 73.3 percent, $p = 0.005$), and the occipital trigger site (trigger site IV) (95.9 percent versus 62.5 percent, $p = 0.0003$). Six patients had exclusively septum or turbinate (site III) surgery, and all failed injections.
Conclusions: Positive botulinum toxin type A response is a significant predictor of migraine surgery success. When injections fail, nonmuscular abnormalities should be considered. (*Plast. Reconstr. Surg.* 131: 751, 2013.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, II.

Migraine headache is one of the most debilitating forms of headache.[1] It afflicts 2 to 15 percent of the world's population and over 35 million Americans, and is responsible for over $14 billion for health care costs and $13 billion for loss of work.[2,3] The World Health Organization ranks migraine headache as the nineteenth most disabling disease and characterizes severe migraine to be as disabling as quadriplegia, psychosis, and dementia.[1,4–6] Nonsurgical treatment of migraines includes avoidance of triggers such as alcohol and caffeine, and pharmacologic control with medications.[7] Botulinum toxin type A has been used off-label since 2000 for the treatment of migraine headache.[8] Since the initial report, multiple small trials have affirmed the effectiveness of botulinum toxin type A in the treatment of migraine headache. However, it was not until the PREEMPT 1 and 2 trials that class 1A evidence was provided that botulinum toxin type A treatment reduces chronic migraine headache impact and improves headache-related quality of life.[9,10] After these evidence-based data, the U.S. Food and Drug Administration approved botulinum toxin type A for the treatment of chronic migraine headache on October 15, 2010. This approval indirectly and to a degree affirms the surgical treatment of migraine headache because the

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physiologic mechanism behind botulinum toxin type A treatment and surgical treatment of migraine headache is probably similar.[11] Both work to decompress peripheral nerves, botulinum toxin type A chemically, whereas surgery mechanically removes anatomical entrapments. In fact, because of this commonality, botulinum toxin type A has long been used as a diagnostic tool in migraine surgery trigger site identification.[12] Although a recent study from our group shows that botulinum toxin type A injection may not be necessary in trigger site identification, approval of botulinum toxin type A by the U.S. Food and Drug Administration for treatment of chronic migraine headache will increase its use among migraine patients.[13]

Individual response to botulinum toxin type A injections varies from no reduction in migraine headache to complete migraine headache elimination. The objective of this study was to determine whether response to botulinum toxin type A injections can serve as a prognosticator for migraine surgery success.

PATIENTS AND METHODS

Institutional review board approval was obtained for this retrospective chart review study. Charts for all patients who had undergone migraine surgery performed by the senior author (B.G.) from 2000 to 2010 were reviewed. Study inclusion criteria included preoperative botulinum toxin type A injection; completion of the Migraine Headache Questionnaire at baseline, after botulinum toxin type A injection; and at least 1-year follow-up after migraine headache surgery. The questionnaire assesses the frequency (migraines per month), duration (in days), and intensity (based on a visual analogue scale from 1 to 10, with 10 being the most severe) of migraine headaches experienced by each patient before and after an intervention (either botulinum toxin type A injection or surgery). The dates of our data collection predated the definition of chronic migraine; we did not retroactively assign this diagnosis. All patients have at least 1-year post–migraine surgery follow-up. Patients with missing Migraine Headache Questionnaires, no preoperative botulinum toxin type A injection, and incomplete follow-up were excluded. Based on the Migraine Headache Questionnaire, the Migraine Headache Index is calculated with the following formula: Migraine Headache Index = migraine headache frequency × migraine headache duration × migraine headache intensity. Success is defined as a minimum of 50 percent reduction in Migraine Headache Index. Patients were divided into two groups following botulinum toxin type A injection: the botulinum toxin type A success group and the botulinum toxin type A failure group. The botulinum toxin type A success group consisted of patients who had greater than 50 percent reduction in Migraine Headache Index. The botulinum toxin type A failure group consisted of patients who had a less than 50 percent reduction in Migraine Headache Index.

Patient information was obtained through a retrospective review of preoperative history and physical examination. Migraine-specific information was collected from initial, post–botulinum toxin type A injection, and postoperative Migraine Headache Questionnaires. Data points included age; sex; location of botulinum toxin type A injection; migraine headache surgery site; and migraine headache frequency, intensity, duration, location, and characterization. Statistical analysis was performed using GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, Calif.). Statistical analysis included mean values and t test. Significance was determined by a value of $p < 0.05$.

Surgical Technique

The operations at each surgical site were performed as described previously.[14,15] For trigger site I, the corrugator supercilii, depressor supercilii, and lateral portion of the procerus were removed using either a transpalpebral or an endoscopic forehead approach. After removal of the muscles, fat from either medial compartment of the upper eyelid or the buccal area is used to protect the decompressed supratrochlear and supraorbital nerves and to fill any defect left by the excised muscles. For trigger site II, approximately 2.5 cm of the zygomaticotemporal branch of the trigeminal nerve was removed using an endoscopic approach. For trigger site III, septoplasty, turbinectomy, or both was performed based on anatomical abnormalities seen on computed tomographic imaging. For trigger site IV, a portion of the semispinalis capitis muscle was removed to decompress the greater occipital nerve bilaterally. The occipital artery was ligated when it was entangled with the nerve. A subcutaneous flap was then placed to separate the remaining muscle and nerve.

RESULTS

One hundred eighty-eight patients met the study inclusion criteria. Of these, 144 patients reported a greater than or equal to 50 percent reduction in Migraine Headache Index following botulinum toxin type A injection (botulinum toxin type A success group) and 44 patients reported a less than 50 percent reduction in Mi-

graine Headache Index after botulinum toxin type A injection (botulinum toxin type A failure group). The two groups were well matched in terms of age (44.6 versus 44.8 years), number of surgical sites (2.46 versus 2.14), and baseline migraine characteristics ($p > 0.05$). Although not statistically significant, the baseline Migraine Headache Index for the botulinum toxin type A success group was higher than that for the botulinum toxin type A failure group (Migraine Headache Index, 203.4 versus 106.5; $p = 0.29$). By definition, the botulinum toxin type A success group had a lower Migraine Headache Index than the botulinum toxin type A failure group following botulinum toxin type A injection (Migraine Headache Index, 8.4 and 76.7, respectively; $p < 0.0001$). Following migraine surgery, the botulinum toxin type A success group had a significantly lower Migraine Headache Index than the botulinum toxin type A failure group (15.7 and 34.6, respectively; $p = 0.009$) (Table 1). The migraine surgery success rate was significantly higher in the botulinum toxin type A success group compared with the botulinum toxin type A failure group (success rate, 90.3 and 72.7 percent, respectively; $p = 0.003$). There was no difference in complete migraine headache elimination between the two groups (39.5 percent for the botulinum toxin type A success group and 27.2 percent for the botulinum toxin type A failure group; $p = 0.25$). Ninety-six of 144 patients (66.7 percent) in the botulinum toxin type A success group had migraine surgery at the same trigger site as the botulinum toxin type A injections, and 28 of 44 patients (63.6 percent) in the botulinum toxin type A failure group had migraine surgery at the same site as the botulinum toxin type A injections. Among patients who had the same botulinum toxin type A injection and surgery site, the migraine surgery success rate was 97.9 percent for the botulinum toxin type A success group and 71.4 percent for the botulinum toxin type A failure group ($p < 0.0001$) (Table 2).

Table 1. Patient Data

	BTA Success Group	BTA Failure Group	*p*
No. of patients	144	44	NA
Age, yr	44.6	44.8	0.95
No. of surgery sites	2.46	2.14	0.12
Baseline MHI	203.4	106.5	0.29
Post-BTA MHI	8.4	76.7	<0.0001
Postsurgery MHI	15.7	34.6	0.009

BTA, botulinum toxin type A; MHI, Migraine Headache Index; NA, not applicable.

Table 2. Migraine Surgery Success and Failure Rates

	BTA Success Group (%)	BTA Failure Group (%)	*p*
MH surgery success	130/144 (90.3)	32/44 (72.7)	0.003
Complete MH elimination	53/144 (39.5)	12/44 (27.2)	0.25
MH surgery success (BTA site = surgery site)	94/96 (97.9)	20/28 (71.4)	<0.0001

BTA, botulinum toxin type A; MH, migraine headache.

Trigger Site Subgroup Analysis

Comparing the location of surgery between the botulinum toxin type A success and failure groups, the botulinum toxin type A success group had more patients with trigger site I surgery (75.7 percent versus 52.3 percent, $p = 0.0009$) and trigger site II surgery (69.4 percent versus 52.3 percent, $p = 0.03$). The two groups were well matched in the number of patients who had trigger site III surgery (50 percent versus 59 percent, $p = 0.29$) and trigger site IV surgery (50 percent versus 50 percent, $p = 1$) (Table 3).

Trigger Site I (Glabella Complex Resection)

One hundred thirty-two patients had surgery at trigger site I. One hundred nine patients belonged to the botulinum toxin type A success group and 23 patients belonged in the botulinum toxin type A failure group. In the botulinum toxin type A success group, 80 patients had botulinum toxin type A injection and migraine surgery at trigger site I. Of those 80 patients, 74 (92.5 percent) reported migraine surgery success. In contrast, in the botulinum toxin type A failure group, nine of 13 patients (69.2 percent) reported success ($p = 0.01$). The migraine headache elimination rate was higher in the botulinum toxin type A success group compared with the botulinum toxin type A failure group (33.7 percent versus 7.6 percent). This difference approaches significance, with a value of $p = 0.058$ (Table 4).

Trigger Site II (Zygomaticotemporal Resection)

One hundred twenty-three patients had surgery at trigger site II. One hundred patients belonged to the botulinum toxin type A success group and 23 patients belonged in the botulinum toxin type A failure group. In the botulinum toxin type A success group, 67 patients had botulinum toxin type A injection and migraine surgery at site II. Of those 67 patients, 64 patients (95.5 percent) reported migraine surgery success. In the botuli-

Table 3. Botulinum Toxin Type A Injection Success and Failure Rates

	BTA Success Group (%)	BTA Failure Group (%)	*p*
Trigger site I (glabellar muscle resection)	109/144 (75.7)	23/44 (52.3)	0.0009
Trigger site II (zygomaticotemporal nerve avulsion)	100/144 (69.4)	23/44 (52.3)	0.036
Trigger site III (septoplasty/turbinectomy)	72/144 (50.0)	26/44 (59.0)	0.29
Trigger site IV (greater occipital nerve decompression)	72/144 (50.0)	22/44 (50)	1.0

BTA, botulinum toxin type A.

Table 4. Trigger Site I: Glabella Complex Resection

	BTA Success Group (%)	BTA Failure Group (%)	*p*
Trigger site I surgery	109	23	
Migraine surgery success (BTA at trigger site I)	74/80 (92.5)	9/13 (69.2)	0.012
Migraine headache elimination (BTA at trigger site I)	27/80 (33.7)	1/13 (7.6)	0.058

BTA, botulinum toxin type A.

num toxin type A failure group, 11 of 15 patients (73.3 percent) reported surgery success ($p = 0.005$). The migraine elimination rate was similar between the two groups: (29.8 percent versus 20 percent, $p = 0.45$) (Table 5).

Trigger Site III (Septoplasty/Turbinectomy)

Seventy-two patients had surgery at trigger site III. Botulinum toxin type A was not injected into trigger site III. Of the 72 patients, 66 had trigger site III surgery in combination with other trigger sites. There were six patients who had exclusively trigger site III surgery, and all six patients failed botulinum toxin type A therapy. The migraine surgery success rate for exclusively trigger site III surgery was 50 percent (three of six patients) (Table 6).

Trigger Site IV (Greater Occipital Nerve Decompression)

Ninety-four patients had surgery at trigger site IV. Seventy-two patients belonged to the botulinum toxin type A success group and 22 patients belonged in the botulinum toxin type A failure group. In the botulinum toxin type A success group, 49 patients had botulinum toxin type A injection and migraine surgery at trigger site IV. Of those 49 patients, 47 (95.9 percent) reported migraine surgery success. In the botulinum toxin type A failure group, 10 of 16 patients (62.5 percent) reported surgery success ($p = 0.0003$). The migraine elimination rate was similar between the two groups (34.7 percent and 25 percent, respectively; $p = 0.48$) (Table 7).

Table 5. Trigger Site II: Zygomaticotemporal Resection

	BTA Success Group (%)	BTA Failure Group (%)	*p*
Trigger site II surgery	100	23	
Migraine surgery success (BTA at trigger site II)	64/67 (95.5)	11/15 (73.3)	0.005
Migraine headache elimination (BTA at trigger site II)	20/67 (29.8)	1/13 (20)	0.45

BTA, botulinum toxin type A.

Table 6. Trigger Site III: Septoplasty/Turbinectomy

	No. of Patients (%)
All patients with trigger site III surgery	72
Patients with *only* trigger site III surgery	6/72 (8.3)
BTA success and *only* trigger site III surgery	0/6 (0)
Migraine surgery success with *only* trigger site III surgery	3/6 (50)

DISCUSSION

Migraine headache is a costly, widespread, and debilitating condition. Traditional theories regarding its cause attribute it to a vascular or central nervous phenomenon. A peripheral trigger point theory for migraine headaches first emerged when frontal migraine symptoms improved with either corrugator supercilii muscle paralysis by botulinum toxin type A injection or corrugator muscle

Table 7. Trigger Site IV: Greater Occipital Nerve Decompression

	BTA Success Group (%)	BTA Failure Group (%)	*p*
Trigger site IV	72	22	
Migraine surgery success (BTA at trigger site IV)	47/49 (95.9)	10/16 (62.5)	0.0003
Migraine headache elimination (BTA at trigger site IV)	17/49 (34.7)	4/16 (25)	0.48

BTA, botulinum toxin type A.

resection.[16,17] It is theorized that the removal of anatomical peripheral compression sites such as the corrugator supercilii muscle will reduce the occurrence of migraine headaches by decreasing peripheral nerve inflammation and excitability. The four most common peripheral trigger sites identified are trigger site I, glabellar muscle group resection in the frontal region; trigger site II, zygomaticotemporal nerve avulsion in the temporal region; trigger site III, septoplasty, turbinectomy in the nasal region; and trigger site IV, greater occipital nerve decompression in the occipital region.[12] For trigger sites I, II, and IV, peripheral branches of the trigeminal nerve are closely associated with potential compression sites, whether it is muscular, vascular, or fascial.[18–24] For trigger site III, intranasal contact and compression points are thought to cause release of pain mediators within the trigeminal system.[24]

The peripheral trigger point for migraine headaches can be deactivated either chemically through botulinum toxin type A injections or mechanically through surgery. Our team and Janis et al. demonstrated that although botulinum toxin type A injection is a potent migraine trigger point deactivator, migraine surgery achieves more permanent and effective results compared with botulinum toxin type A injection. Patients often reports worsening migraine headaches 2.5 to 3 months after injection, which corresponds to the return of dynamic muscle contraction.[25,26] In addition to providing temporary reduction in migraine headaches, botulinum toxin type A injections also play an important role in migraine surgery. Botulinum toxin type A can be used to identify potential migraine surgery trigger sites. However, we recently demonstrated that a thorough history and physical examination is equivalent to botulinum toxin type A injection in diagnosing potential trigger sites. In the senior author's (B.G.) practice, the identification of trigger sites no longer depends on botulinum toxin type A injection results. As such, patients who did not respond to botulinum toxin type A may still undergo migraine headache surgery if an appropriate history and physical examination indicates a potential trigger site.[13] Instead of using botulinum toxin type A as a diagnostic tool, we propose that the botulinum toxin type A injection response can serve as a powerful prognosticator for migraine surgery success, as demonstrated in this study.

The majority of patients who present for migraine surgery have had prior botulinum toxin type A injection, for either diagnostic or therapeutic purposes. This number will only increase given recent approval of use of botulinum toxin type A by the U.S. Food and Drug Administration for therapeutic migraine treatment. In the senior author's database, the majority of patients (53.3 percent) have had botulinum toxin type A before surgery. Patients who received therapeutic botulinum toxin type A injections, particularly from neurologists, differ from patients who received diagnostic botulinum toxin type A injections in that therapeutic botulinum toxin type A injections are administered in multiple nonspecific sites per visit in the head and neck region. Diagnostic botulinum toxin type A injections, in contrast, are administered at one trigger site per visit based on the constellation of symptoms. If necessary, subsequent trigger sites are injected up to a maximum of three sites. Diagnostic botulinum toxin type A injection identifies and confirms potential trigger sites.[12] Of the 188 patients, 124 (65.9 percent) reported botulinum toxin type A injection at the same site(s) as migraine surgery. The 64 patients who reported differing botulinum toxin type A injection and surgery site had trigger site III surgery.

Overall, migraine surgery success is higher in patients who respond favorably to botulinum toxin type A injections, regardless of whether botulinum toxin type A injection and surgery are at the same site (surgery success rate, 90.3 percent and 72.7 percent, respectively; $p = 0.03$). It is important to clarify that we included patients who did not receive botulinum toxin type A at the surgery site, and these were largely the patients who had migraine headache surgery at trigger site III (rhinogenic).

The relationship between botulinum toxin type A response and migraine surgery response is magnified when patients with the same botulinum toxin type A injection and surgery site were examined. In this subgroup of patients, the success rate of migraine surgery is significantly higher in the botulinum toxin type A success group compared with the botulinum toxin type A failure group (surgery success rate, 97.9 and 71.4 percent, respectively; $p < 0.0001$).

Another potential confounder is that the botulinum toxin type A success group and the botulinum toxin type A failure group were not well matched in terms of surgery site. Significantly more trigger site I and II operations were performed in the botulinum toxin type A success group. Over 75 percent of patients in the botulinum toxin type A success group had trigger site I surgery compared with only 52.3 percent of patients in the botulinum toxin type A failure group

($p = 0.0009$). Similarly, 69.4 percent of patients had trigger site II surgery in the botulinum toxin type A success group compared with only 52.3 percent of patients in the botulinum toxin type A failure group. Operations at trigger sites I and II have been associated with increased migraine surgery success.[27] To control for this confounder, the different surgical sites were analyzed individually.

For patients who had both botulinum toxin type A injection and surgery at trigger site I, the surgery success rate was significantly higher in patients who responded to botulinum toxin type A injection than in those who did not (92.5 and 69.2 percent, respectively; $p = 0.012$). Interestingly, botulinum toxin type A success is also associated with a higher migraine elimination rate with surgery (33.7 percent versus 7.6 percent). Although not statistically significant, the p value approaches significance at 0.058.

Cadaveric anatomical studies by Janis et al. demonstrated four branching patterns of the supraorbital nerve. In 78 percent of specimens, the supraorbital nerve (branching patterns I through III) demonstrated an intimate association with the corrugator supercilii muscle. The remaining 22 percent of specimens demonstrated branching pattern IV: the supraorbital nerve branched cephalad to the muscle without any muscle fiber association.[19] We postulate that the group that responds to botulinum toxin type A injections consists mostly of patients with supraorbital branching patterns I through III, where the glabella muscle complex is the main source of compression. Therefore, glabella myectomy will likely yield successful migraine headache reduction, if not elimination. However, if the patient does not respond to botulinum toxin type A injection at trigger site I, supraorbital branching pattern IV should be considered and an alternative abnormality at trigger site I such as supratrochlear nerve irritation or the need for a supraorbital foraminotomy should be evaluated.[28] For patients who had botulinum toxin type A injection and surgery at trigger site II, the surgery success rate was again significantly higher in patients who responded to botulinum toxin type A injection than in those who did not (surgery success, 95.5 and 73.3 percent, respectively; $p = 0.005$). However, the elimination rate was similar between to the two groups. There is substantial (>80 percent) overlap between patients who had trigger site I and trigger site II surgery. It is therefore difficult to distinguish the effect of botulinum toxin type A on trigger site I versus site trigger II.

There were only six patients with exclusively trigger site III surgery. All six patients failed to respond to botulinum toxin type A. This supports the theory that nasal abnormality must be considered when patients fail to respond to botulinum toxin type A. In addition, even with surgery in this site (trigger site III), the success rate is not as high as the other sites because multiple structures could play a role in triggering rhinogenic migraine headaches.

Among trigger site IV surgery patients, those who responded to botulinum toxin type A injection at trigger site IV reported a significantly higher migraine success rate than those who did not (surgery success rates, 95.9 and 62.5 percent, respectively; $p = 0.0003$). The greater occipital nerve can be irritated by both musculofascial compression and a mechanical interaction with the occipital artery. Cadaveric studies identified multiple musculofascial compression sites as the nerve courses along the semispinalis and the trapezius muscle. The occipital artery is identified to cross the greater occipital nerve distal to the musculofascial compression sites.[21] We hypothesize that patients who respond to botulinum toxin type A injections at trigger site IV consist mainly of those with musculofascial compression of the greater occipital nerve, where resection of the semispinalis will most likely increase the surgery success rate. Patients who failed botulinum toxin type A therapy may have additional compression sites such as an intertwining occipital artery.[21] These patients most likely had incomplete decompressions. Patients with occipital artery or fascial compression sites will not respond to botulinum toxin type A injection, and if those sites are not addressed in trigger site IV surgery, migraine headache will not improve. It is especially important to identify possible fascial and occipital artery compression points in trigger site IV patients who fail botulinum toxin type A injection.

Migraine surgery is a rapidly evolving field. With growing clinical experience, better understanding of anatomical variances, and identification of new trigger sites, migraine surgical techniques are constantly being developed and refined. In the past, botulinum toxin type A has aided surgeons in the identification of trigger sites. We propose that botulinum toxin type A can serve not only as a prognosticator of migraine surgery success at the injected site, but also as an indicator for potential additional nonmuscular compression sites in the patient who fails botulinum toxin type A therapy.

CONCLUSIONS

Botulinum toxin type A injection can serve as a powerful prognosticator of migraine surgery success in trigger sites I, II, and IV. For patients who fail botulinum toxin type A therapy, nasal abnormality, as suggested in the senior author's algorithm[12] (along with supraorbital foraminotomy, fasciotomy, concomitant artery removal, and other anatomical variations), should be considered, in addition to nonsurgical migraine triggers.

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