JPRAS Open 38 (2023) 152–162

Contents lists available at ScienceDirect

JPRAS Open

journal homepage: www.elsevier.com/locate/jpra

Functional outcomes between headache surgery and targeted botox injections: A prospective multicenter pilot study

Jeffrey E. Janis[a,*], Jason Hehr[a], Maria T. Huayllani[a], Ibrahim Khansa[a], Lisa Gfrerer[c], Kaitlin Kavanagh[a], Pamela Blake[d,e], Yevgeniya Gokun[b], William G. Austen Jr[c]

[a] *Department of Plastic and Reconstructive Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA*
[b] *Center for the Biostatistics, Department of Biomedical Informatics, The Ohio State University Wexner Center, Columbus, OH, USA*
[c] *Division of Plastic and Reconstructive Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Mass, USA*
[d] *Headache Center of River Oaks, Houston, TX, USA*
[e] *University of Texas Health Science Center, Houston, TX, USA*

ARTICLE INFO

Article history:
Received 14 September 2023
Accepted 20 September 2023
Available online 30 September 2023

Keywords:
Migraine headache
Migraine surgery
Botulinum neurotoxin A
Functional outcomes
MHI
MIDAS
MWPLQ
MSQ

ABSTRACT

Introduction: Chronic migraine headaches (MH) are a principal cause of disability worldwide. This study evaluated and compared functional outcomes after peripheral trigger point deactivation surgery or botulinum neurotoxin A (BTA) treatment in patients with MH.

Methods: A long-term, multicenter, and prospective study was performed. Patients with chronic migraine were recruited at the Ohio State University and Massachusetts General Hospital and included in each treatment group according to their preference (BTA or surgery). Assessment tools including the Migraine Headache Index (MHI), Migraine Disability Assessment Questionnaire (MIDAS) total, MIDAS A, MIDAS B, Migraine Work and Productivity Loss Questionnaire-question 7 (MWPLQ7), and Migraine-Specific Quality

* Corresponding author at: 915 Olentangy River Road, Columbus, OH 43212, USA.
E-mail address: jeffrey.janis@osumc.edu (J.E. Janis).
Social media: (J.E. Janis)

https://doi.org/10.1016/j.jpra.2023.09.009

of Life Questionnaire (MSQ) version 2.1 were used to evaluate functional outcomes. Patients were evaluated prior to treatment and at 1, 2, and 2.5 years after treatment.

Results: A total of 44 patients were included in the study (surgery=33, BTA=11). Patients treated surgically showed statistically significant improvement in headache intensity as measured on MIDAS B ($p = 0.0464$) and reduced disability as measured on MWPLQ7 ($p = 0.0120$) compared to those treated with BTA injection. No statistical difference between groups was found for the remaining functional outcomes. Mean scores significantly improved over time independently of treatment for MHI, MIDAS total, MIDAS A, MIDAS B, and MWPLQ 7 ($p<0.05$). However, no difference in mean scores over time was observed for MSQ.

Conclusions: Headache surgery and targeted BTA injections are both effective means of addressing peripheral trigger sites causing headache pain. However, lower pain intensity and work-related disabilities were found in the surgical group.

Introduction

Migraine headaches (MH) are a leading cause of disability worldwide,[1] with a global prevalence exceeding 13%.[2] The etiology of MH relates to the activation and sensitization of trigeminovascular neurons that subsequently release vasoactive peptides and induce local inflammation.[3-6] Compressive forces overlying extracranial nerves, including muscular contraction, fascial bands and/or thickened, fibrotic fascia, bony compression, or intersecting/intertwining blood vessels, can lead to sensitization of trigeminal and occipital nerves, leading to the release of pro-inflammatory neuropeptides, resulting in sterile meningitis and MH.[7] The demonstration of interconnections between the peripheral and central nervous systems running in cranial sutures support the evidence that peripheral nerves can play a role in these headaches.[8,9] As evidence supporting the peripheral nerve theory of MH continues to grow, so does the focus on interventions targeted at these pathways, specifically deactivation of extracranial nerve trigger sites, especially in patients who have failed traditional/medical treatments.[10-22]

Botulinum neurotoxin A (BTA) injections temporarily paralyze muscles causing peripheral nerve compression that helps identify trigger sites for surgical release.[14-21,23-26] BTA has also been shown to reduce mechanosensitivity of peripheral nerve fibers[27] and to alter inflammatory gene expression in calvarium periosteum.[28] Level I data have supported the efficacy of BTA in treating MH,[29-32] and Botox (Allergan, Dublin, Ireland) currently holds FDA approval for on-label use in this regard since 2010. Alternatively, surgical deactivation of peripheral trigger sites has previously shown superior clinical outcomes compared to standard medical management.[22,33,34] Anatomic descriptions of common trigger sites and the step-wise approach to the surgical management of these sites have been previously described,[35-46] but only a few retrospective studies evaluated the efficacy of migraine surgery compared to BTA treatment in patients with MH.[32,33] Our multicenter, prospective study aimed to compare functional outcomes related to long-term targeted BTA injections versus surgical release of peripheral trigger sites as a treatment of MH refractory to medical treatment.

Materials and methods

An Institutional Review Board (IRB) approval through the Ohio State University, Wexner Medical Center (OSU), and authorization for external collaboration at Harvard Medical School, Massachusetts General Hospital (MGH), were obtained. The clinical trial was also registered in ClinicalTrials.gov

(Identifier: NCT02351544). Our inclusion criteria consisted of patients who: 1) have been diagnosed by a board-certified neurologist with chronic migraine headaches (≥ 15 days per month) as dictated by Food and Drug Administration indication for botulinum neurotoxin, 2) had MH related to a trigger site at the location of a branch of a cranial nerve (frontal, temporal, and occipital), 3) responded to targeted diagnostic BTA injection[47] or anesthetic nerve block,[48] and 4) previously failed two of three classes of preventative migraine medications. Our exclusion criteria included patients deemed by a neurologist to not have MH, patients with systemic conditions that contraindicated surgery (such as unstable coronary artery disease, uncontrolled diabetes mellitus, etc.), patients with migraines related to inferior turbinate hypertrophy or septal deviation, patients with hypersensitivity to any botulinum toxin preparation or any components in the formulation, patients with infection at the proposed injection site for BTA, and those with trigger points at lesser occipital or auriculotemporal trigger sites (as these sites were not amenable to injection with Botox).

Trigger site confirmation was determined with the combined use of multiple methods[10,49]: 1) constellation of symptoms and physical examination, 2) local anesthetic nerve block injected into the specific trigger point in those patients presenting with active pain at the time of a clinic visit,[48] 3) diagnostic BTA injection into a specific trigger point,[47] 4) handheld Doppler, and 5) pain sketches.[50] After confirming the above inclusion criteria, patients were prospectively enrolled in the study. All patients underwent standard workup to determine if they had peripheral trigger sites that could undergo surgical deactivation. Any candidate who was deemed a surgical candidate was offered two options: surgical intervention or non-surgical targeted Botox injections to alleviate symptoms associated with peripheral trigger sites. Education on both arms was provided, and patients were then assigned into the arm of their preference. Patients in the BTA arm underwent targeted injections at 3-month intervals from the time of enrollment. Typically, this entailed dilution of a 100-unit vial of Botox with 4cc of preserved saline, and injection of 25 units per greater occipital nerve (50 units total if bilateral), 12.5 units per supraorbital/supratrochlear site (25 units total, if bilateral), and 18.75 units per zygomaticotemporal (37.5 units total, if bilateral). Patients assigned to the surgical arm underwent surgical deactivation of the involved peripheral nerves. Patients who had surgery did not receive BTA after surgery.

Functional outcomes were prospectively measured using a variety of measures, described below, including the Migraine Headache Index (MHI),[11] the Migraine Disability Assessment Questionnaire (MIDAS),[51] the number of MH in the last 3 months (MIDAS A), and pain associated with MH (MIDAS B), the Migraine Work and Productivity Loss Questionnaire[52] - Question 7 (MWPLQ7) and the Migraine-Specific Quality of Life Questionnaire (MSQ) version 2.1.[53]

MHI[11] is a numerical value calculated by multiplying the severity (1–10 numerical rating scale), duration (fraction of 24 h), and frequency (days per month) of migraine headaches.

MIDAS questionnaire[51] was developed to quantify the effect of headaches on patients' daily functionality in the past 3 months. It consists of five questions related to paid work or school, household work, and leisure time. A total score of 0–5 corresponds to little or no disability, 6–10 points refers to mild disability, 11–20 points mean moderate disability, and more than 21 points represent severe disability (MIDAS total). In addition, there are two questions regarding the number of days with MH (MIDAS A), and the intensity of pain associated with MH in the last three months (MIDAS B). For MIDAS total, the higher the numeric response, the greater the overall impact of MH. MIDAS A and B do not factor into MIDAS total score, therefore, all three were examined independently.

MWPLQ[52] has nine questions that evaluate the impact of migraine and migraine therapy on paid work and productivity loss. Question #7 from the MWPLQ (MWPLQ7) was the most frequently and consistently answered with meaningful responses and did not depend on questions #1–6, 8–9. Therefore, MWPLQ7 was analyzed independently, and the remaining questions were not included in the final analysis. Question #7 assesses the difficulty of 18 work-related activities caused by the most recent MH or migraine headache treatment. Each item in question 7 has the following options: 0 ('no difficulty'), 1 ('a slight amount'), 2 ('some'), 3 ('quite a bit'), 4 ('a great deal'), 5 ('so much difficulty, could not do at all'), and 6 ('does not apply to my work'). To quantify difficulty, a total sum score of these 18 items including only options 0 to 5 is obtained. A higher MWPLQ7 summed score reveals a higher effect of MH on work and productivity.

MSQ version 2.1[53] is a 14-item questionnaire that evaluates the long-term perceived impact of MH on health-related quality of life over the past 4 weeks. Three dimensions of functional status specific to MH are measured: 1) the role restrictive, consisting of a 7-item dimension that measures the degree to which MH limits the performance of normal activities; 2) the role preventive, a dimension that consists of four items measuring the degree to which normal activities are interrupted by MH; and 3) the emotional dimension consisting of three items that measure the emotional impact of MH. Responses per item include a 6-point scale: 'none of the time,' 'a little bit of the time,' 'some of the time,' 'a good bit of the time,' 'most of the time,' and 'all of the time.' Each option is assigned a score of 1 to 6, respectively. Each domain is scored independently as a sum of items and rescaled from a 0 to 100 scale, with higher scores indicating better quality of life. MSQ survey was analyzed in totality. A higher MSQ sum reflects patient improvement in quality of life.

Each of the above outcome measures was prospectively collected at the time of enrollment (baseline), 1 year, 2 years, and 2.5 years of follow-up from the initiation of treatment.

Statistical analysis

Descriptive statistics, such as frequency and percentages, were displayed for gender (male or female), treatment (BTA or surgery), and clinical site (OSU or MGH). Descriptive statistics, such as mean, standard deviation, and range, were reported for age (collected at baseline). Patient functional scores were obtained from MHI, MIDAS total, MIDAS A, MIDAS B, MWPLQ7, and MSQ.

Natural logarithm was applied to each of the six outcomes before the outcome was modeled because they were highly skewed. A constant of one was added to outcome values before applying natural log function so as to include raw values of zeros.

Linear mixed models with a random effect for patients were used to evaluate the changes in each functional outcome between two different treatments over time, including the interaction between treatment and time. These models were used to account for correlation between repeated measurements on the same patient and to account for missing data across time points. Tables 2a-7a depict mean score comparisons of functional outcomes between targeted BTA and surgery groups. If significance was found in time independently of treatment group, Tables 2b-6b attempted pairwise comparisons between various time frames to determine significance at specific time points. P-values for both the main and interaction effects of time and treatment were reported for each model. Tukey's post hoc method was used to adjust for pairwise comparisons. For ease of interpretation, raw means and SDs are presented for each time point within specific treatment.

Analyses were performed using SAS v9.4 (SAS Institute; Cary, NC; www.sas.com). Statistical significance was defined as two-sided alpha$<$0.05.

Results

A total of 44 patients met our inclusion criteria. Twenty (45.5%) patients were recruited at MGH and 24 (54.5%), at OSU. Thirty-nine (88.6%) patients were female and five (11.4%) were male. The mean age of participants was 43 years (SD=13.2, range=18–73). Eleven (25%) patients received targeted BTA treatment, whereas 33 (75%) patients underwent surgical treatment (Table 1). All patients who received BTA treatment ($n = 11$) were enrolled at OSU. Of the 33 patients who underwent surgery, 13 were enrolled at OSU and 20 were enrolled at Massachusetts.

None of the regression analyses showed a statistically significant interaction effect between time and treatment when modeling various outcomes of interest (Tables 2–7). When functional outcomes were compared between surgical treatment and BTA independently of time, patients who underwent surgery had statistically significant lower mean scores in MIDAS B (4.03 vs 6.30, $p = 0.0464$, Table 5a) and MWPLQ 7 (15.43 vs 38.26, $p = 0.0120$, Table 6a) compared to those treated with targeted BTA injection. However, no statistically significant difference was found among treatment groups independently of time for the other functional outcomes.

The mean scores significantly improved after treatment over time independently of the type of treatment for MHI ($p<0.0001$, Tables 2a and 2b), MIDAS total ($p<0.0001$, Tables 3a and 3b), MIDAS A ($p<0.0001$, Tables 4a and 4b), MIDAS B ($p = 0.0191$, Tables 5a and 5b), and MWPLQ 7 ($p = 0.0001$,

Table 1
Demographic characteristics.

Variable	BTA (n = 11, 25%)	Surgery (n = 33, 75%)	Total (N = 44)
Age			
Mean (SD)	39.1 (14.3)	43.8 (12.7)	42.6 (13.2)
Range	19–73	18–66	18–73
Gender			
Female	10 (90.9%)	29 (87.9%)	39 (88.6%)
Male	1 (9.1%)	4 (12.1%)	5 (11.4%)
Site			
MGH	0 (0%)	20 (60.6%)	20 (45.5%)
OSU	11 (100%)	13 (39.4%)	24 (54.5%)

Table 2a
Multivariable results modeling the outcome of MHI.

Variable	BTA		Surgery		Total Mean (95% CI)	P-value
	N	Mean (95% CI)	n	Mean (95% CI)		
Time Frame						
Baseline	11	64.14 (24.46–165.62)	13	109.89 (45.74–262.09)	83.99 (43.90–159.87)	
1 year	11	7.81 (2.44–21.53)	12	3.73 (0.94–10.53)	5.45 (2.38–11.33)	
2 years	10	8.74 (2.69–24.72)	10	5.54 (1.52–15.94)	6.98 (3.04–14.75)	
2.5 years	3	4.62 (0.18–25.74)	2	1.28 (0.00–13.70)	2.58 (0.06–11.06)	
Total		12.31 (4.90–29.04)		8.40 (3.17–20.15)		
Time						<0.0001
Treatment						0.5401
Time*Treatment						0.2984

Table 2b
Six pairwise comparisons between various time frames (unadjusted and adjusted p-values) for the outcome of MHI.

Comparison	Unadjusted p-value	Adjusted p-value (adjusted for Tukey's post hoc method)
Baseline vs 1 year	<0.0001	<0.0001
Baseline vs 2 years	<0.0001	<0.0001
Baseline vs 2.5 years	<0.0001	<0.0001
1-year vs 2 years	0.5460	0.9288
1-year vs 2.5 years	0.3415	0.7721
2 years vs 2.5 years	0.2007	0.5690

Table 3a
Multivariable results modeling the outcome of MIDAS Total.

Variable	BTA		Surgery		Total Mean (95% CI)	P-value
	N	Mean (95% CI)	n	Mean (95% CI)		
Time Frame						
Baseline	11	38.63 (14.96–97.43)	32	71.15 (41.33–122.00)	52.47 (30.56–89.60)	
1 year	11	17.05 (6.27–43.82)	28	8.84 (4.62–16.22)	12.35 (6.81–21.73)	
2 years	10	10.84 (3.62–29.33)	24	7.60 (3.76–14.54)	9.09 (4.79–16.59)	
2.5 years	3	10.25 (1.48–50.08)	10	10.55 (3.98–25.79)	10.40 (3.80–26.09)	
Total		16.57 (7.06–37.31)		15.29 (9.32–24.74)		
Time						<0.0001
Treatment						0.8677
Time*Treatment						0.1682

Table 3b
Six pairwise comparisons between various time frames (unadjusted and adjusted p-values) for the outcome of MIDAS Total.

Comparison	Unadjusted p-value	Adjusted p-value (adjusted for Tukey's post hoc method)
Baseline vs 1 year	<0.0001	<0.0001
Baseline vs 2 years	<0.0001	<0.0001
Baseline vs 2.5 years	0.0007	0.0041
1-year vs 2 years	0.3414	0.7742
1-year vs 2.5 years	0.7270	0.9852
2 years vs 2.5 years	0.7854	0.9928

Table 4a
Multivariable results modeling the outcome of MIDAS A.

Variable	BTA		Surgery		Total Mean (95% CI)	P-value
	N	Mean (95% CI)	n	Mean (95% CI)		
Time Frame						
Baseline	11	45.88 (20.41–101.63)	30	61.10 (37.86–98.22)	52.95 (33.18–84.17)	
1 year	11	12.36 (5.10–28.26)	27	9.06 (5.18–15.35)	10.59 (6.31–17.38)	
2 years	10	9.70 (3.77–23.01)	24	8.21 (4.55–14.28)	8.93 (5.17–14.99)	
2.5 years	3	10.86 (2.36–40.83)	11	8.30 (3.71–17.34)	9.50 (4.13–20.49)	
Total		15.79 (7.46–32.32)		14.21 (9.20–21.67)		
Time						<0.0001
Treatment						0.8023
Time*Treatment						0.6248

Table 4b
Six pairwise comparisons between various time frames (unadjusted and adjusted p-values) for outcome of MIDAS A.

Comparison	Unadjusted p-value	Adjusted p-value (adjusted for Tukey's post hoc method)
Baseline vs 1 year	<0.0001	<0.0001
Baseline vs 2 years	<0.0001	<0.0001
Baseline vs 2.5 years	<0.0001	<0.0001
1-year vs 2 years	0.5158	0.9143
1-year vs 2.5 years	0.7845	0.9927
2 years vs 2.5 years	0.8785	0.9987

Table 5a
Multivariable results modeling the outcome of MIDAS B.

Variable	BTA		Surgery		Total Mean (95% CI)	P-value
	N	Mean (95% CI)	n	Mean (95% CI)		
Time Frame						
Baseline	11	7.09 (4.48–10.93)	29	6.83 (5.18–8.93)	6.96 (5.34–9.00)	
1 year	11	6.42 (4.03–9.94)	27	3.19 (2.28–4.36)	4.58 (3.43–6.02)	
2 years	10	5.32 (3.22–8.47)	24	3.60 (2.56–4.96)	4.40 (3.25–5.86)	
2.5 years	3	6.47 (2.75–13.87)	11	3.23 (1.93–5.09)	4.62 (2.80–7.30)	
Total		6.30 (4.32–9.01)		4.03 (3.18–5.04)		
Time						0.0191
Treatment						0.0464
Time*Treatment						0.2157

Table 5b
Pairwise comparisons between various time frames as well between two treatments (unadjusted and adjusted p-values) for outcome of MIDAS B.

Comparison	Unadjusted p-value	Adjusted p-value (adjusted for Tukey's post hoc method)
Baseline vs 1 year	0.0093	0.0446
Baseline vs 2 years	0.0060	0.0300
Baseline vs 2.5 years	0.0975	0.3437
1-year vs 2 years	0.8096	0.9950
1-year vs 2.5 years	0.9727	1.0000
2 years vs 2.5 years	0.8475	0.9974
BTA vs Surgery	0.0464	0.0464

Table 6a
Multivariable results modeling the outcome of MWPLQ 7.

Variable	BTA		Surgery		Total Mean (95% CI)	P-value
	N	Mean (95% CI)	n	Mean (95% CI)		
Time Frame						
Baseline	10	57.17 (29.50–109.92)	18	44.98 (27.57–73.00)	50.72 (33.63–76.23)	
1 year	10	40.44 (20.73–78.03)	16	16.03 (9.34–27.06)	25.57 (16.67–38.95)	
2 years	9	34.68 (17.21–68.87)	11	7.63 (3.82–14.47)	16.55 (10.25–26.38)	
2.5 years	3	26.62 (8.55–78.91)	7	9.79 (4.30–20.99)	16.26 (8.11–31.72)	
Total		38.26 (21.89–66.34)		15.43 (10.13–23.27)		
Time						0.0001
Treatment						0.0120
Time*Treatment						0.1136

Table 6b
Pairwise comparisons between various time frames as well between two treatments (unadjusted and adjusted p-values) for outcome of MWPLQ 7.

Comparison	Unadjusted p-value	Adjusted p-value (adjusted for Tukey's post hoc method)
Baseline vs 1 year	0.0045	0.0223
Baseline vs 2 years	<0.0001	0.0002
Baseline vs 2.5 years	0.0018	0.0094
1-year vs 2 years	0.0933	0.3288
1-year vs 2.5 years	0.2061	0.5801
2 years vs 2.5 years	0.9623	1.0000
BTA vs Surgery	0.0120	0.0120

Tables 6a and 6b). In fact, the number of migraines quarterly prior to treatment in the targeted BTA arm, as reported on the MIDAS A question, was 45.88 prior to initiation of targeted BTA injections; this number reduced to 12.86 at 1 year. The benefit was maintained for 2.5 years, with MIDAS A score of 10.86, representing a reduction in quarterly migraine days of 76.32%. The response to trigger point deactivation surgery was even more pronounced: the pre-surgical quarterly number of migraine days as recorded on the MIDAS A question was 61.10 and reduced to 9.06 at one year. This benefit was maintained at 2.5 years following treatment, with MIDAS A score of 8.30, representing an 86.41% reduction in the number of quarterly migraine days as reported on the MIDAS A question. The reduction in the number of quarterly migraine days was statistically significant independently of the group of treatment ($p<0.0001$, Table 4a).

Table 7
Multivariable results modeling the outcome of MSQ.

Variable	BTA		Surgery		Total Mean (95% CI)	P-value
	n	Mean (95% CI)	n	Mean (95% CI)		
Time Frame						
Baseline	11	43.30 (24.78–75.12)	33	49.28 (35.79–67.73)	46.20 (33.53–63.51)	
1 year	11	55.05 (31.62–95.30)	30	60.61 (43.41–84.47)	57.76 (41.83–79.62)	
2 years	10	61.12 (34.23–108.53)	26	43.42 (30.27–62.10)	51.53 (36.63–72.32)	
2.5 years	3	74.30 (26.08–208.37)	13	37.73 (22.66–62.40)	53.00 (29.61–94.26)	
Total		57.38 (38.14–86.07)		47.05 (37.57–58.84)		
Time						0.7691
Treatment						0.3965
Time*Treatment						0.4598

In addition, MHI, MIDAS total, and MWPLQ7 differed significantly between baseline and each of three follow-up times (1, 2, and 2.5 years) while MIDAS B differed significantly only between baseline and each of these two follow-up times (1 and 2 years) using adjusted p-values from Tukey's post hoc method.

None of the effects such as time, treatment, and interaction between time and treatment included in the regression modeling the outcome of MSQ was statistically significant (Table 7).

Discussion

MH causes over 112 million workdays lost, costs American employers approximately $13 billion annually, and accounts for direct medical annual costs of roughly $1 billion.[54] Given the economic impact of this condition and the debilitating consequences of a vast number of patients worldwide suffering from chronic MH, continued research into the optimal treatment of these patients is warranted.

Studies have demonstrated the efficacy of peripheral trigger point deactivation surgery in MH refractory to medical treatment.[11-22] A functional improvement over time has been previously reported in patients who undergo surgery.[55] Our study replicates the finding of a significant and sustained reduction in migraine headache frequency. No study, however, has yet compared long-term outcomes of surgical deactivation of peripheral trigger sites with targeted BTA injections in a prospective manner and across multiple centers. Our study sought to identify differences in functional outcomes between these two treatment options for patients with chronic MH refractory to medical treatment.

The MIDAS score has been demonstrated to be directly associated with frequency of MH.[56] On the other hand, MWPLQ which measures work loss and difficulty, has been correlated with migraine severity and functional ability.[52] In our study, both surgical intervention and targeted BTA treatments provided significant improvement in chronic migraine as reflected by reduction in scores on the MIDAS questionnaire, as well as other screening tools. In fact, the MIDAS B and MWPLQ7 mean scores significantly improved in patients who underwent surgery compared to those treated with targeted BTA independently of time, suggesting better outcomes after surgery. These findings are consistent with the continued pain relief more commonly found in surgical patients who may require, less follow-up visits, as surgery does not rely on the temporal effect of BTA injections. The expected waxing and waning pain secondary to the timing of subsequent BTA injections may have impacted the perception of disability and health-related quality of life. Our results align with Janis et al.,[32] who retrospectively compared MHI between patients who underwent long-term Botox injections and migraine surgery at more than 1 year of follow-up. The authors found that both treatments were effective compared with baseline; however, surgery demonstrated a significantly greater MHI improve-

ment compared to long-term Botox.[32] Similarly, Bajaj et al[57] compared the functional outcomes of 13 patients who underwent peripheral trigger point deactivation surgery using peripheral neurectomies with those of 13 patients who had medical management using bupivacaine block at the trigger site. They found a statistically significant improvement in MHI, MIDAS, visual analog score, and pain self-efficacy questionnaire at 6 months after surgery.[57] Although these findings might indicate a potential increased benefit for surgery compared with targeted BTA, one cannot infer that this, in fact, occurred, due to our low sample size.

In our study, both treatment options showed significant improvement over time for almost all outcome measures, except for MSQ, compared with baseline scores. This might be related to the subjective perception of patients assessed by the MSQ, as headaches may still be considered to significantly and negatively impact a patient's life with even a single severe migraine episode in the prior 4 weeks. In addition, the number of patients enrolled in the study might also contributed to the lack of significance. This finding should be explored in more detail in further studies with a greater sample size.

When evaluating functional improvement over time, chronicity and cost of treatment must be considered. BTA injection may be related to higher costs as a result of multiple office visits due to the short duration of the pain relief (approximately 3 months) and product costs.[26] Schoenbrunner et al[26] detailed the mean cost of peripheral trigger site deactivation surgery of $10,303 compared to long-term targeted BTA treatment at an estimated $36,071. Their results found that surgical intervention becomes more cost effective in patients requiring more than 6.75 years of treatment. Similarly, Faber et al[58] analyzed the costs associated with surgical treatment of MH in 89 patients. The authors found a total median cost reduction of $3949.70 per year at 5 years postoperatively. Therefore, expected treatment duration and overall cost of treatment should be considered when informing patients of treatment options. Furthermore, since surgery appears to have a similar improvement in functional outcomes, patients who elect BTA as their first treatment and do not have successful results may be offered surgical treatment subsequently.

Our study is not without limitations. The small sample size and possible attrition bias due to a lower response rate at longer follow-up (out to 2.5 years) limited our ability to determine significant long-term differences. Additionally, patients undergoing targeted BTA injection treatment or surgical deactivation of peripheral trigger sites likely represent a portion of the most severely impaired cohort of all patients suffering from MH, which might have led to a potential selection bias. Self-selection bias may have also limited our study, as patients were not independently randomized into each arm. Therefore, patients electing a specific treatment might have reported improved outcomes secondary to a subconscious pressure to demonstrate that they made the correct choice. Furthermore, some of the questionnaires applied to patients asked about their perceptions of a certain period in the past, which could have resulted in recall bias. In addition, the time at which the surveys were applied differed between patients. This might have influenced the outcomes and explained the lack of difference between treatments at each time of follow-up. Finally, this study did not allow the distinction of outcomes by trigger site between BTA and surgical decompression. However, we believe this pilot study is an important first step to overcome possible limitations in future studies with a larger sample size more patients enrolled from more sites.

Conclusion

Both targeted BTA injections and nerve deactivation provide a dramatic reduction in migraine headache frequency. Peripheral trigger point deactivation surgery has similar functional outcomes as compared to targeted BTA injections. In general, surgical trigger site deactivation appears to have decreased patient-reported pain associated with MH and decreased difficulty in work-related activities compared to BTA treatment, although this may be related to the waxing and waning of pain in the BTA cohort as compared to the more consistent results produced by surgery. BTA injections and surgical decompression showed functional improvement in MHI, MIDAS total, and MIDAS A after treatment at 1, 2, and 2.5 years of follow-up. MSQ was not statistically different between treatments or over time. Further long-term studies are required to examine maintained benefits. Length of treatment and cost associated should be considered when discussing treatment options with patients suffering from chronic MH.

Conflict of Interest

Dr. Janis receives royalties from Springer Publishing and Thieme Publishers. Dr. Austen Jr. receives royalties from Cytrellis biosystems, Durvena, Volumina, Arctic Fox, and Sientra. Drs. Hehr, Huayllani, Khansa, Gfrerer, Kavanagh, Blake, and Ms. Gokun have nothing to disclose.

Funding

None of the authors have received funding for this article.

Ethical approval

An Institutional Review Board approval through The Ohio State University, Wexner Medical Center and authorization for external collaboration at Harvard Medical School, Massachusetts General Hospital were obtained. The clinical trial was also registered in ClinicalTrials.gov (Identifier: NCT02351544).

References

1. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1204–1222.
2. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2018;17(11):954–976.
3. Ashina M. Migraine. *N Engl J Med*. 2020;383(19):1866–1876.
4. Calandre EP, Hidalgo J, García-Leiva JM, Rico-Villademoros F. Trigger point evaluation in migraine patients: An indication of peripheral sensitization linked to migraine predisposition? *Eur J Neurol*. 2006;13(3):244–249.
5. Olesen J. Clinical and pathophysiological observations in migraine and tension-type headache explained by integration of vascular, supraspinal and myofascial inputs. *Pain*. 1991;46(2):125–132.
6. Kidd RF, Nelson R. Musculoskeletal dysfunction of the neck in migraine and tension headache. *Headache*. 1993;33(10):566–569.
7. Buzzi MG, Tassorelli C, Nappi G. Peripheral and central activation of trigeminal pain pathways in migraine: Data from experimental animal models. *Cephalalgia*. 2003;23(Suppl 1):1–4.
8. Gfrerer L, Wenjie Xu L, Austen W, et al. OnabotulinumtoxinA alters inflammatory gene expression and immune cells in chronic headache patients. *Brain*. 2021.
9. Perry CJ, Blake P, Buettner C, et al. Upregulation of inflammatory gene transcripts in periosteum of chronic migraineurs: Implications for extracranial origin of headache. *Ann Neurol*. 2016;79(6):1000–1013.
10. Gfrerer L, Austen Jr WG, Janis JE. Migraine Surgery. *Plast Reconstr Surg Glob Open*. 2019;7(7):e2291.
11. ElHawary H, Barone N, Baradaran A, Janis JE. Efficacy and safety of migraine surgery: A systematic review and meta-analysis of outcomes and complication rates. *Ann Surg*. 2022;275(2):e315–e323.
12. Huayllani MT, Janis JE. Migraine surgery and determination of success over time by trigger site: A systematic review of the literature. *Plast Reconstr Surg*. 2022.
13. Chen G, You H, Juha H, et al. Trigger areas nerve decompression for refractory chronic migraine. *Clin Neurol Neurosurg*. 2021;206:106699.
14. Janis JE, Barker JC, Javadi C, Ducic I, Hagan R, Guyuron B. A review of current evidence in the surgical treatment of migraine headaches. *Plast Reconstr Surg*. 2014;134(4 Suppl 2):131s–141s.
15. Baldelli I, Mangialardi ML, Raposio E. Site V surgery for temporal migraine headaches. *Plast Reconstr Surg-Glob Open*. 2020;8(6):e2886.
16. Baldelli I, Mangialardi ML, Salgarello M, Raposio E. Peripheral occipital nerve decompression surgery in migraine headache. *Plast Reconstr Surg-Glob Open*. 2020;8(10):e3019.
17. Bink T, Duraku LS, Ter Louw RP, Zuidam JM, Mathijssen IMJ, Driessen C. The cutting edge of headache surgery: A systematic review on the value of extracranial surgery in the treatment of chronic headache. *Plast Reconstr Surg*. 2019;144(6):1431–1448.
18. Mathew P. A critical evaluation of migraine trigger site deactivation surgery. *Neurology*. 2014;82(10).
19. Nagori SA, Jose A, Roychoudhury A. Surgical management of migraine headaches: A systematic review and meta-analysis. *Ann Plast Surg*. 2019;83(2):232–240.
20. Robinson IS, Salibian AA, Alfonso AR, Lin LJ, Janis JE, Chiu ES. Surgical management of occipital neuralgia: A systematic review of the literature. *Ann Plast Surg*. 2021;86(3):S322–S331.
21. Wormald JCR, Luck J, Athwal B, Muelhberger T, Mosahebi A. Surgical intervention for chronic migraine headache: A systematic review. *JPRAS Open*. 2019;20:1–18.
22. Janis JE, Dhanik A, Howard JH. Validation of the peripheral trigger point theory of migraine headaches: Single-surgeon experience using botulinum toxin and surgical decompression. *Plast Reconstr Surg*. 2011;128(1):123–131.
23. Lee M, Monson MA, Liu MT, Reed D, Guyuron B. Positive botulinum toxin type a response is a prognosticator for migraine surgery success. *Plast Reconstr Surg*. 2013;131(4):751–757.
24. Nahabet E, Janis JE, Guyuron B. Neurotoxins: expanding uses of neuromodulators in medicine–headache. *Plast Reconstr Surg*. 2015;136(5 Suppl):104s–110s.
25. Hehr JD, Schoenbrunner AR, Janis JE. The use of botulinum toxin in pain management: Basic science and clinical applications. *Plast Reconstr Surg*. 2020;145(3):629e–636e.

26. Schoenbrunner AR, Khansa I, Janis JE. Cost-effectiveness of long-term, targeted OnabotulinumtoxinA versus peripheral trigger site deactivation surgery for the treatment of refractory migraine headaches. *Plast Reconstr Surg*. 2020;145(2):401e–406e.
27. Burstein R, Zhang X, Levy D, Aoki KR, Brin MF. Selective inhibition of meningeal nociceptors by botulinum neurotoxin type A: Therapeutic implications for migraine and other pains. *Cephalalgia*. 2014;34(11):853–869.
28. Gfrerer L, Xu W, Austen W, et al. OnabotulinumtoxinA alters inflammatory gene expression and immune cells in chronic headache patients. *Brain*. 2022;145(7):2436–2449.
29. Aurora SK, Winner P, Freeman MC, et al. OnabotulinumtoxinA for treatment of chronic migraine: Pooled analyses of the 56-week PREEMPT clinical program. *Headache*. 2011;51(9):1358–1373.
30. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: A randomized, double-blind, placebo-controlled trial. *Headache*. 2005;45(4):293–307.
31. Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD. Botulinum toxin type a for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: A randomized double-blind, placebo-controlled study. *Headache*. 2005;45(4):315–324.
32. Janis JE, Barker JC, Palettas M. Targeted peripheral nerve-directed OnabotulinumtoxinA injection for effective long-term therapy for migraine headache. *Plast Reconstr Surg Glob Open*. 2017;5(3):e1270.
33. Guyuron B, Reed D, Kriegler JS, Davis J, Pashmini N, Amini S. A placebo-controlled surgical trial of the treatment of migraine headaches. *Plast Reconstr Surg*. 2009;124(2):461–468.
34. Guyuron B, Kriegler JS, Davis J, Amini SB. Five-year outcome of surgical treatment of migraine headaches. *Plast Reconstr Surg*. 2011;127(2):603–608.
35. Janis JE, Ghavami A, Lemmon JA, Leedy JE, Guyuron B. The anatomy of the corrugator supercilii muscle: part II. Supraorbital nerve branching patterns. *Plast Reconstr Surg*. 2008;121(1):233–240.
36. Fallucco M, Janis JE, Hagan RR. The anatomical morphology of the supraorbital notch: clinical relevance to the surgical treatment of migraine headaches. *Plast Reconstr Surg*. 2012;130(6):1227–1233.
37. Janis JE, Hatef DA, Hagan R, et al. Anatomy of the supratrochlear nerve: implications for the surgical treatment of migraine headaches. *Plast Reconstr Surg*. 2013;131(4):743–750.
38. Janis JE, Hatef DA, Thakar H, et al. The zygomaticotemporal branch of the trigeminal nerve: Part II. Anatomical variations. *Plast Reconstr Surg*. 2010;126(2):435–442.
39. Janis JE, Hatef DA, Ducic I, et al. Anatomy of the auriculotemporal nerve: variations in its relationship to the superficial temporal artery and implications for the treatment of migraine headaches. *Plast Reconstr Surg*. 2010;125(5):1422–1428.
40. Chim H, Okada HC, Brown MS, et al. The auriculotemporal nerve in etiology of migraine headaches: compression points and anatomical variations. *Plast Reconstr Surg*. 2012;130(2):336–341.
41. Janis JE, Hatef DA, Ducic I, et al. The anatomy of the greater occipital nerve: Part II. Compression point topography. *Plast Reconstr Surg*. 2010;126(5):1563–1572.
42. Janis JE, Hatef DA, Reece EM, McCluskey PD, Schaub TA, Guyuron B. Neurovascular compression of the greater occipital nerve: implications for migraine headaches. *Plast Reconstr Surg*. 2010;126(6):1996–2001.
43. Chepla KJ, Oh E, Guyuron B. Clinical outcomes following supraorbital foraminotomy for treatment of frontal migraine headache. *Plast Reconstr Surg*. 2012;129(4):656e–662e.
44. Liu MT, Chim H, Guyuron B. Outcome comparison of endoscopic and transpalpebral decompression for treatment of frontal migraine headaches. *Plast Reconstr Surg*. 2012;129(5):1113–1119.
45. Guyuron B, Kriegler JS, Davis J, Amini SB. Comprehensive surgical treatment of migraine headaches. *Plast Reconstr Surg*. 2005;115(1):1–9.
46. Gfrerer L, Dayan E, Austen Jr WG. Trigger-site deactivation surgery for nerve compression headaches. *Plast Reconstr Surg*. 2021;147(6):1004e–1021e.
47. ElHawary H, Kavanagh K, Janis JE. The positive and negative predictive value of targeted diagnostic botox injection in nerve decompression migraine surgery. Accepted for publication to. *Plast Reconstr Surg J*. 2023.
48. Rangwani SM, Hehr JC, Janis JE. Clinical effectiveness of peripheral nerve blocks for diagnosis of migraine trigger points. *Plast Reconstr Surg*. 2021;148(6):992e–1000e.
49. Guyuron B, Nahabet E, Khansa I, Reed D, Janis JE. The current means for detection of migraine headache trigger sites. *Plast Reconstr Surg*. 2015;136(4):860–867.
50. Gfrerer L, Hansdorfer MA, Ortiz R, et al. Patient Pain sketches can predict surgical outcomes in trigger-site deactivation surgery for headaches. *Plast Reconstr Surg*. 2020;146(4):863–871.
51. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) questionnaire to assess headache-related disability. *Neurology*. 2001;56(6 Suppl 1):S20–S28.
52. Davies GM, Santanello N, Gerth W, Lerner D, Block GA. Validation of a migraine work and productivity loss questionnaire for use in migraine studies. *Cephalalgia*. 1999;19(5):497–502.
53. Martin BC, Pathak DS, Sharfman MI, et al. Validity and reliability of the migraine-specific quality of life questionnaire (MSQ Version 2.1). *Headache*. 2000;40(3):204–215.
54. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: disability and economic costs. *Arch Intern Med*. 1999;159(8):813–818.
55. Okmen K, Dagistan Y, Dagistan E, Kaplan N, Cancan E. Efficacy of the greater occipital nerve block in recurrent migraine type headaches. *Neurol Neurochir Pol*. 2016;50(3):151–154.
56. Shapiro RE, Martin AA, Bhardwaj S, et al. Relationships between headache frequency, disability, and disability-related unemployment among adults with migraine. *J Manag Care Spec Pharm*. 2023;29(2):197–209.
57. Bajaj J, Doddamani R, Chandra SP, et al. Comparison of peripheral neurectomy vs. medical treatment for migraine: A randomized controlled trial. *Neurol India*. 2021;69(Supplement):S110–s115.
58. Faber C, Garcia RM, Davis J, Guyuron B. A socioeconomic analysis of surgical treatment of migraine headaches. *Plast Reconstr Surg*. 2012;129(4):871–877.