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The Positive and Negative Predictive Value of Targeted Diagnostic Botox Injection in Nerve Decompression Migraine Surgery

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Short running title: BOTOX injections for trigger site identification

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ABSTRACT

Introduction: Nerve decompression surgery is an effective treatment modality for patients who suffer from migraines. Botulinum toxin type A (BOTOX) injections have been traditionally used as a method to identify trigger sites, however there is a paucity in data regarding its diagnostic efficacy. The goal of this study was to assess the diagnostic capacity of BOTOX in successfully identifying migraine trigger sites and predicting surgical success.

Methods: A sensitivity analysis was performed on all patients receiving BOTOX for migraine trigger site localization followed by a surgical decompression of affected peripheral nerves. Positive and negative predictive values were calculated.

Results: A total of 40 patients met our inclusion criteria and underwent targeted diagnostic BOTOX injection followed by a peripheral nerve deactivation surgery with at least three months follow-up. Patients with successful BOTOX injections (defined as at least 50% improvement in Migraine Headache Index (MHI) scores post injection) had significantly higher average reduction in migraine intensity (56.7% vs 25.8%; p=0.020, respectively), frequency (78.1% vs 46.8%; p=0.018, respectively), and MHI (89.7% vs 49.2%; p=0.016, respectively) post-surgical deactivation. Sensitivity analysis shows that the use of BOTOX injection as a diagnostic modality for migraine headaches has a sensitivity of 56.7% and a specificity of 80.0%. The positive predictive value is 89.5% and the negative predictive value is 38.1%.

Conclusion: Diagnostic targeted BOTOX injections have a very high positive predictive value. It is therefore a useful diagnostic modality that can help identify migraine trigger sites and improve pre-operative patient selection.

INTRODUCTION

Migraines are common neurovascular disorders affecting over one billion people worldwide.[1] In the United States (US) alone, over 50 million patients suffer with migraines. While not the most common type of headache, it is associated with the most personal and societal suffering with estimates reaching as high as 45 million years lived with disability due to migraines globally.[1]

Migraines have been traditionally perceived as a central neurovascular disease that was often treated with acute analgesics and abortive medications.[2] However, several key anatomical studies have elucidated how specific peripheral nerve trigger sites can play a major role in the development and exacerbation of migraine headaches by demonstrating the connection between the central and peripheral nervous system, and hence supported the hypothesis that peripheral nerve compression is a possible contributing factor of this disease.[3-16]

Peripheral nerve deactivation surgery, or "migraine surgery", has steadily evolved evidence to support its efficacy over the last two decades.[17] Several studies have demonstrated the clinical efficacy and safety of nerve deactivation surgery to cement it as an acceptable treatment modality.[17, 18] However, a recent study by Gfrerer et al. has demonstrated a binary distribution of outcomes, where patients either significantly improve, or fail to improve after surgery, with very few intermediate outcomes.[19] Therefore, a thorough pre-operative assessment and accurate diagnosis is of paramount importance to ensure optimal patient selection and improved surgical outcomes. Current methods for detection of migraine trigger sites have been previously described and begin with asking the patient to identify the most frequent site from which headaches originate, followed by exploration of that site with a physical exam and handheld Doppler to evaluate for vascular-related trigger sites.[20] If the patient has an active

headache during the visit, the site is preferentially injected with local anesthetic and a positive response to the nerve block (defined as at least a 50% improvement in pain) confirms presence of a trigger site, with a positive predictive value of 0.89.[21] If the patient does not have an active headache at the time of clinical presentation, a diagnostic nerve block cannot be performed. For these patients, a targeted BOTOX injection can be considered, and positive responses again support the presence of a trigger site.

While BOTOX injections are generally performed in areas with known anatomical trigger sites containing muscle as a possible source of compression, mechanism of symptom relief is likely multifactorial and not limited to local muscle paralysis alone. Theoretical mechanisms of action include modulation of neurotransmitter release, inhibition of peripheral nociceptive fiber sensitization and neurogenic inflammation, and subsequent decrease in central sensitization.[22-25] Therefore, headaches caused by peripheral nerve compression by structures other than muscle may be improved with BOTOX injection.

While the injection of targeted BOTOX is commonly used to confirm trigger sites pre-operatively, its positive and negative predictive values have yet to be determined. To that end, the goal of this study was to quantitatively assess the diagnostic capacity of BOTOX in successfully identifying peripheral nerve migraine trigger sites.

METHODS

Study Design

This retrospective single institution chart review was performed on all patients receiving BOTOX for migraine trigger site localization, followed by a surgical decompression of affected peripheral nerves by the senior author (JEJ) from 2014-2021, who had at least 3 months follow-up with 100% compliance for all postoperative visits and 100% completed patient reported

outcome documentation forms. All included patients had neurologist-diagnosed migraine headaches and failed conservative non-surgical treatment. Patients were not actively receiving any other therapeutic intervention during the study, excluding oral medications. Exclusion criteria included any patient who did not have a surgical deactivation, did not have at least 3 months follow-up with 100% compliance with all postoperative visits, or 100% compliance with filling out all postoperative patient-reported outcomes documentation. Institutional Review Board approval was obtained before commencing the study.

BOTOX administration and workup

Patients were eligible for a BOTOX injection if they were able to describe quantifiable pain localized to a known anatomical trigger site that contained muscle as a possible source of compression, but no active pain at the time of clinical presentation (whereby a diagnostic nerve block, rather than BOTOX, was performed for given active pain at the time of presentation). Eligible patients underwent a targeted peripheral nerve directed BOTOX injection at the site of their migraine initiation.[26] Additional trigger sites were also injected in a sequential manner if symptoms remained as per Guyuron's et al's original algorithm.[27] Trigger sites included: greater occipital nerve (GON), supraorbital nerve (SON), supratrochlear nerve (STN), and zygomaticotemporal nerve (ZTN).

Diluted BOTOX at a concentration of 25 units/ml was used (4cc preserved saline per 100 unit vial, freshly reconstituted on the day of the clinic visit). A total of 0.5 ml (12.5 units) was used for each unilateral SON and STN, while 1ml (25 units) and 0.75 ml (18.75 units) were used for each unilateral GON and ZTN, respectively (Figure 1). Please refer to Janis et al. for full details on targeted BOTOX administration.[26] These dosages differ from those described in the PREEMPT trial, based on which BOTOX received on-label FDA approval for treatment of

chronic migraine headaches in 2010, in that these utilize a targeted, anatomically-based approach, and have been previously shown to be safe and efficacious in these locations with low risk of serious adverse outcomes.[28] Specifically, the PREEMPT technique describes administration of 155 units of BOTOX across 31 sites and representing 7 head and neck muscle groups, whereas the targeted approach used in the current paper involves injection of higher doses in more targeted locations with a lower cumulative injection dose, in contrast to injection of lower doses in a broader distribution.[26, 28]

Patients were then asked to report their migraine intensity (1-10), frequency (number of migraines per month), and duration (as a fraction of 24 hours), one month post BOTOX injection. Migraine headache index (MHI) was calculated by multiplying the aforementioned factors. For the purpose of this study, a BOTOX injection was initially defined to be successful if it decreased MHI by over 50%. We then altered the threshold of success to be defined as over 70% and over 90% reduction in MHI post-injection. In the senior author's practice, patients with unsuccessful BOTOX injections are not re-injected at the initial site. In patients with unsuccessful BOTOX injections, the decision to proceed with surgery despite a negative BOTOX test was made based on various additional components of their individual presentations, including high suspicion based on constellation of symptoms,[29] physical exam findings, positive Doppler sites, imaging, and response to nerve blocks.

Surgical protocol and follow up

Post BOTOX injection, all patients underwent a peripheral nerve deactivation surgery based upon headache characteristics and the previously identified trigger sites. Prior to surgery, patients were asked to report their baseline headache outcomes. All patients were followed-up for at least 3 months.

Outcomes

Patient demographic outcomes including age, sex, and race were recorded. Migraine outcomes including migraine intensity, frequency, duration, and MHI were recorded preoperatively and at 3- and 12-months post operatively. A successful surgery was defined as a decrease in MHI of over 50%.

Statistical analysis

In addition to descriptive analysis, post-operative changes were assessed using generalized estimating equations (GEE) models to assess the overall change in migraine outcomes pre- and post-operatively. Furthermore, post-hoc measures with Bonferroni corrections were performed to assess for any change between 3- and 12-months follow-up. Data is presented as estimated marginal means ± standard errors. Wilcox Sign test were used when the assumption for normal distributions was not met, and data is presented as median and interquartile ranges (IRQs). Sensitivity analyses were performed and repeated at different BOTOX injection success thresholds (>50%, >70%, and >90%). Positive predictive value (PPV) was calculated to evaluate the efficacy of BOTOX injections in diagnosing migraine trigger sites. PPV was defined as the probability that a patient with a successful BOTOX injection at a location has migraine symptoms due to pathology at that location and is treatable with a surgical decompression. True positives were defined as patients who had a successful BOTOX injection who underwent a successful surgery. False positives were patients who had a successful BOTOX injection but an unsuccessful surgery. All statistical analyses were performed using SPSS 25.0 (IBM, NY, USA). Significance was pre-determined and set at $p < 0.05$.

RESULTS

A total of 40 patients met our inclusion criteria and underwent targeted diagnostic BOTOX injection followed by a peripheral nerve deactivation surgery. Of these patients, 30 (75.0%) were females while the remaining 10 (25.0%) were males. The average age was 45.2±14.2 (Table 1). At baseline, the patients' average migraine duration was 0.77±0.12, average migraine intensity was 7.49±0.28, average migraine frequency was 24.1±1.75, and MHI was 131.0±18.2.

After surgical deactivation, all MHI parameters significantly improved at 3 months (n=40) and 12 months follow-up (n=22) ($p<0.001$). Out of the 18 participants that were not included in the 12 months follow-up analysis, 11 were lost to follow-up and 7 had their surgeries within one year of the time of analysis and therefore were not included in the 12 months analysis. At 3 months follow-up, migraine duration decreased to 0.34±0.07 ($p=0.001$), migraine intensity decreased to 4.44±0.55 ($p<0.001$), migraine frequency decreased to 9.22±1.84 ($p<0.001$), and average MHI decreased to 42.6±13.2 ($p<0.001$). Post-hoc repeated measures with Bonferroni correction showed no significant change in all outcomes between 3 and 12 months. Specifically, migraine duration non significantly changed from 0.34±0.07 to 0.25±0.09 ($p=0.621$). Similarly, migraine intensity non significantly changed from 4.44±0.55 to 3.30±0.76 ($p=0.185$). Migraine frequency non significantly changed from 9.22±1.84 to 8.42±2.49 ($p=1.0$). Finally, MHI non significantly changed from 42.6 ±13.2 to 21.7±11.1 ($p=0.206$) (Table 1).

Out of the 40 included patients, 19 (47.5%) had a successful BOTOX injection. Amongst these patients, all their headache outcomes significantly improved after surgery. Specifically, migraine duration decreased from 0.5 (0.9) to 0.01 (0.3); ($p=0.006$), migraine intensity decreased

from 8 (2.5) to 3.5 (7.0); (p<0.001), migraine frequency decreased from 30 (14.0) to 0.67 (9.0); (p<0.001), and MHI decreased from 105 (157.5) to 0.42 (2.3); (p<0.001).

On the other hand, 21 patients had unsuccessful BOTOX injections. All the headache outcomes improved after surgery. Specifically, migraine duration decreased from 1 (0.8) to 0.17 (1.0); (p=0.015), migraine intensity decreased from 8 (1.0) to 7 (6.5); (p=0.018), migraine frequency decreased from 30 (16.0) to 8 (29.8); (p<0.001), and MHI decreased from 128 (216.2) to 21 (138.0); (p<0.001). An analysis of the patients that were lost to follow up showed a similar distribution of successful to unsuccessful BOTOX injections; five patients (45.5%) had successful injections while six (55.5%) had unsuccessful injection. (Table 2)

Patients with successful BOTOX injections had significantly higher mean reductions in migraine intensity (56.7% vs 25.8%; p=0.020, respectively), frequency (78.1% vs 46.8%; p=0.018, respectively), and overall MHI (89.7% vs 49.2%; p=0.016) post-operatively. While they also experienced higher average reductions in migraine duration (78.3% vs 37.0%; p=0.167), the reductions were not statistically significant.

Surgery success was defined as a post-operative reduction in MHI by at least 50%. Out of the 19 patients that had a successful BOTOX injection (over 50% reduction in MHI post injection), 17 had a successful surgery. On the other hand, out of the 21 patients that had an unsuccessful BOTOX injection, only 13 had a successful surgery. Sensitivity analysis demonstrates that the use of BOTOX injection as a diagnostic modality for migraine headaches has a sensitivity of 56.7% and a specificity of 80.0%. The positive predictive value is 89.5% and the negative predictive value is 38.1%. By changing the definition of a successful BOTOX injection to over 70% reduction in MHI post injection, the PPV and NPV slightly changed to 93.3% and 36.0%, respectively. Similarly, if a successful BOTOX injection was defined over

90% reduction in MHI post injection, PPV and NPV further decreased to 87.5% and 28.1%, respectively (Table 3 and Figure 2).

DISCUSSION

The results of this study suggest there is diagnostic benefit of pre-operative targeted BOTOX injections in patients suffering from migraine headaches. Our study shows that on average, patients who have a successful BOTOX injection (defined as at least 50% improvement in MHI) have improved outcomes post-surgical deactivation compared to those who have unsuccessful BOTOX injection. Furthermore, this is the first study to demonstrate the high positive predictive value of pre-operative targeted diagnostic BOTOX injections, which further reinforces its importance in the pre-operative workup for migraine headaches.

Peripheral nerve deactivation surgery for headaches is a prospering field with excellent outcomes and outstanding safety profile.[18] The results of this study show that surgery significantly improves outcomes and is successful in approximately 80% of cases (regardless of the success of BOTOX injections), which is in line with previous literature.[30, 31] The fact that the majority of patients experience significant improvements after this surgery, as is demonstrated in this study and previous literature,[19] lends further support to the importance of pre-operative patient selection in order to continue improving outcomes in this field.

While BOTOX injections have been used as a treatment modality for migraine headaches since their FDA approval for on label use in October 2010, their use as diagnostic modality predates that.[21] Alongside a thorough clinical examination and trigger site mapping, BOTOX injections and peripheral nerve blocks have been recently used to better identify trigger sites. In the current study, patients who had a successful BOTOX injection had significantly larger reductions in migraine frequency and intensity and MHI compared to their counterparts who had

unsuccessful BOTOX injections. While surgery was successful in 75% of all patients in this study, the success rate in the positive BOTOX group was significantly higher at approximately 89.5%. In other words, approximately 9 out of 10 patients suffering from migraines, who have a successful diagnostic BOTOX injection pre-operatively, will improve after surgery. This supports the utility of BOTOX as a reliable diagnostic tool for identifying patients that will respond to surgery. A recent systematic review evaluating the efficacy of migraine surgeries demonstrated that 68.5-100% of patients report improvement after migraine surgery, with our data falling within this reported range.[18]

On the other hand, the negative predictive value of the BOTOX injection is only 38.1%, which means that over half of the patients that had an unsuccessful BOTOX injection will still improve after surgery. It is also important to note that changing the threshold of BOTOX injection success from a reduction in MHI of 50% to 70% or 90%, only slightly reduced the positive and negative predictive values. Based on these results, the authors of this paper recommend the routine use of diagnostic BOTOX injections in the pre-operative assessment as it can help identify patients who are more likely to benefit from the surgery (regardless of how significant the improvement in outcomes are post-injection). Moreover, it is important to note that an unsuccessful BOTOX injection does not completely eliminate the possibility of compression at the specified trigger site. Therefore, in patients with an unsuccessful BOTOX injection, we recommend further diagnostic modalities such as peripheral nerve blocks, which have been recently shown to also have a high positive predictive value, as well as other tests such as constellation of symptoms, Doppler, CT scan, and pain sketches.[20, 21, 31]

This study is not without limitations. The first of which is the relatively small sample size and loss to follow-up (n=22 at 12 months), which might have contributed to limited

generalizability and lack of statistical significance in some of the migraine outcomes between patients who had successful and unsuccessful injections. However, we have performed post hoc analyses which showed no significant changes in any of the outcomes between 3 and 12 months post operatively, which suggests that patients lost to follow up had similar outcomes to those retained at 12 months post op. Furthermore, as mentioned above, patients who presented with active pain during clinic were preferentially offered a nerve block (not part of this study), while those without active pain were offered a diagnostic targeted BOTOX injection and were eligible for this study. This can potentially affect the generalizability of results as we did not include patients who had active pain. However, the patient population included in this study is generally representative of the overall American population experiencing migraine headaches, in accordance with previous studies, and significant findings are therefore likely applicable to a larger population.[32]

Moreover, many patients had multiple trigger sites addressed, as well as BOTOX injections at multiple sites (guided by constellation of symptoms), which limits our assessment of the diagnostic accuracy of BOTOX injections of specific independent trigger sites. However, in the author's experience, the diffusion capacity of BOTOX makes it difficult to address some sites singularly (i.e. SON and STN).[33] An additional limitation is that the reported MHI is not stratified by location of symptoms, but overall symptom quality. Future studies evaluating specific trigger sites will be useful in determining if the efficacy of BOTOX as a diagnostic modality is affected by location of injection.

CONCLUSION

BOTOX injections are a useful diagnostic modality that can help identify migraine trigger sites and improve pre-operative patient selection. BOTOX injections have very high positive predictive values which means that patients who improve after BOTOX will most likely have positive outcomes post peripheral nerve deactivation surgery. Moreover, patients who do not experience significant improvements after BOTOX injections can still be surgery candidates (low negative predictive value) and therefore warrant further preoperative workup.

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Table and figure legends

Table 1: Participants' demographics and migraine outcomes pre- and post-operatively

P values represent the overall trend assessed using generalized estimating equation models

Values presented as estimated marginal means ± standard error

Table 2: Migraine outcomes stratified based on success of BOTOX injection

Success of BOTOX injection defined as at least 50% reduction in MHI post injection

Wilcox Sign test was used to assess post-operative changes in migraine outcomes.

Data presented as median (interquartile ranges) (IQR).

Table 3: Positive and negative predictive values based on different thresholds of BOTOX injection success

PPV: positive predictive value

NPV: negative predictive value

*Successful surgery was defined as at least 50% improvement in MHI post-operative

Figure 1: BOTOX injection sites, nerves and structured involved, and amount injected per site

Figure 2: Receiver Operator Curve showing sensitivity and specificity for BOTOX injections in predicting migraine surgical success

Blue line: Botox injection success defined as an injection that caused MHI to be decreased by over 50 percent

Red line: Botox injection success defined as an injection that caused MHI to be decreased by over 70 percent

Green line: Botox injection success defined as an injection that caused MHI to be decreased by over 90 percent

	Pre-operative (n=40)	3 months (n=40)	12 months (n=22)	P value
Age (mean ± SD)	45.2±14.2	45.2±14.2	45.0±13.7	-
Ethnicity				
- Caucasian	39	39	21	-
- Unknown	1	1	1	-
Migraine duration	0.77±0.12	0.34±0.07	0.25±0.09	<0.001
Migraine intensity	7.49±0.28	4.44±0.55	3.30±0.76	<0.001
Migraine frequency	24.1±1.75	9.22±1.84	8.42±2.49	<0.001
Migraine headache index	131.0±18.2	42.6+13.2	21.7±11.1	<0.001

Table 1: Participants' demographics and migraine outcomes pre- and post-operatively

P values represent the overall trend assessed using generalized estimating equation models

Values presented as estimated marginal means ± standard error

Outcome	Successful BOTOX injection (n=19)			Unsuccessful BOTOX injection (n=21)		
	Pre op	Post op	P value	Pre op	Post op	P value
Migraine duration	0.5 (0.9)	0.01 (0.3)	0.006	1 (0.8)	0.17 (1.0)	0.015
Migraine intensity	8 (2.5.0)	3.5 (7.0)	<0.001	8 (1.0)	7 (6.5)	0.018
Migraine frequency	30 (14.0)	0.67 (9.0)	<0.001	30 (16.0)	8 (29.8)	<0.001
Migraine headache index	105 (157.5)	0.42 (2.3)	<0.001	128 (216.2)	21 (138.0)	<0.001

Table 2: Migraine outcomes stratified based on success of BOTOX injection

Success of BOTOX injection defined as at least 50% reduction in MHI post injection

Wilcox Sign test was used to assess post-operative changes in migraine outcomes.

Data presented as median (interquartile ranges) (IQR).

	Threshold of success of BOTOX injection		
	50%	70%	90%
Total number of patients with successful surgery	30	30	30
Total number of patients with unsuccessful surgery	10	10	10
Patients with successful injection (of whom had successful surgery)	19 (17)	15 (14)	8 (7)
Patients with unsuccessful injection (of whom had unsuccessful surgery)	21 (8)	25 (9)	32 (9)
PPV	89.5	93.3	87.5
NPV	38.1	36.0	28.1

Table 3: Positive and negative predictive values based on different thresholds of BOTOX injection success

PPV: positive predictive value

NPV: negative predictive value

*Successful surgery was defined as at least 50% improvement in MHI post-operative

Figure 1

Injection site	Botox injection pattern	Nerves involved	Structured involved	Units of BOTOX injected
SON/STN		Supraorbital and supratrochlear nerves	Glabellar muscles, foramina, and fascial bands	12.5 units (0.5 cc) unilaterally
ZTN		Zygomaticotemporal branch of cranial nerve	Temporalis muscle, deep temporal fascia, and surrounding vessels	18.75 units (0.75 cc) unilaterally
GON		Greater occipital nerve	Semispinalis capitis, fascial bands, and occipital artery	25 units (0.5 cc) unilaterally

Figure 2