Prospective, Multi-Center Evaluation of the Efficacy of Migraine Surgery

Research Protocol

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I. Background and rationale

According to the peripheral trigger theory of migraine headaches, nociceptive inputs from irritated or compressed cranial nerve branches can lead to neurovascular changes in the brain that cause migraine headaches.[1-3] Advanced treatments aimed at deactivating the peripheral trigger points can be administered to patients who have failed medical management of migraines. Those accepted advanced treatments include botulinum toxin A injection in order to temporarily paralyze muscles causing nerve compression, and surgery to release those compression points permanently. An advantage of surgery is the ability to release non-muscular causes of nerve compression, such as fascial bands or intersecting arteries.

Botulinum toxin A injection into trigger sites has been shown in multiple studies to be effective at reducing the frequency and severity of migraine headaches,[4-6] and is a very commonly administered treatment for refractory migraines. It is approved by the FDA for the treatment of chronic migraines.

Similarly, surgical decompression of trigger sites has previously been shown to have superior clinical outcomes to medical management, through a randomized, blinded controlled-trial performed at Case Western Reserve in 2009.[7] Patients either received actual decompression of the trigger sites, or sham surgery (exposure and visualization of the trigger sites, without decompression). At one-year follow-up, the group who underwent actual surgery demonstrated a statistically higher proportion with significant improvement in their migraines (83.7% vs. 57.7%, $p=0.014$), and with complete elimination of their migraines (57.1% vs. 3.8%, $p<0.001$). Several other reports have confirmed the good clinical outcomes of surgery demonstrated in this trial,[6,8] and surgical decompression is now commonly performed by several surgeons around the United States.

Prognostic factors predicting the success of surgical decompression in migraine headache treatment include older age of migraine onset, visual symptoms/aura, and 4-site decompression. Factors predicting failure of surgery include excessive operative blood loss, and surgery on only one or two trigger sites.[9]

One criticism of the studies on migraine surgery has been that most of the results have originated from the same institution (Case Western Reserve), and from the same author (Guyuron). While several studies at other institutions have demonstrated positive outcomes of migraine surgery,[6] these have only included a small number of patients.

In addition, the sham surgery randomized-controlled trial has been criticized for not clarifying any prior treatments that patients had undergone before migraine surgery, and for not showing how medication use patterns changed after surgery. Another criticism of that study was the fact that patients were examined by neurologists before the study but not after the study, and that surgery was performed on some patients with episodic migraines, who are known to not benefit from botulinum toxin. It is unclear what migraine types are most likely to benefit from surgical decompression.

Our goal is to perform a multi-center, prospective trial to demonstrate the effectiveness of migraine surgery, which would address the criticisms mentioned above. The main aim is to demonstrate that the positive results demonstrated by Guyuron *et al* are reproducible at other institutions and by other surgeons using similar techniques on different patient populations.

II. Objectives

Our goals in this study are:

1. To evaluate the effectiveness of surgical decompression in migraine headaches prospectively, using validated instruments, and to compare it to the effectiveness of a botulinum toxin injection protocol
    a. Our hypothesis is that migraine surgery decreases the frequency and severity of migraine headaches significantly, as measured by

validated questionnaires, and that the reduction is greater and more sustainable than that seen with a botulinum toxin injection protocol

2. To determine which types of migraine headaches benefit most from surgical decompression and/or botulinum toxin injection
3. To identify prognostic factors for the success or failure of surgical decompression in migraine headache
    a. These have been demonstrated in a previous study,[9] but have not evaluated in a multi-center fashion.
4. To compare the long-term direct and indirect costs in patients with migraine headaches undergoing botulinum toxin A injections versus surgical decompression
    a. We hypothesize that, over the long-term, surgical decompression is more cost-efficient than a botulinum toxin injection protocol

III. Procedures

a. Research design

This is a **prospective, multi-center** evaluation of the short, medium and long-term efficacy of surgical decompression in migraine headaches, comparing it to the efficacy of a botulinum toxin injection protocol.

b. Sample

Inclusion criteria:

-Patients with migraines related to a trigger site at the location of a branch of a cranial nerve (frontal, temporal, occipital)

-Patients with chronic migraine (≥15 days per month) as dictated by the FDA indication for botulinum, and as diagnosed by a board-certified neurologist

Exclusion criteria:

-Patients deemed by the senior author or the neurologist to not have migraine headaches, but an alternative diagnosis

-Patients with systemic conditions that make them poor candidates for surgery (coronary artery disease, uncontrolled diabetes mellitus, etc…)

-Patients with migraines related to inferior turbinate hypertrophy or septal deviation

-Patients with a frontal, temporal or occipital trigger point who do not respond to a diagnostic botulinum toxin injection

-Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation

-Infection at the proposed injection site for botulinum

Sample size (power analysis)

Since there are several endpoints in this study, the required sample size can be calculated in several ways:

-Using efficacy as an endpoint:

In Janis *et al*,[6] patients undergoing botulinum toxin injections had an average improvement in their Migraine Headache Index of 87.5%. In comparison, patients undergoing surgery had an average improvement of 96.6%.

Assuming a standard deviation of 20%, an alpha error of 5%, and a power of 80%, the required sample size using this method is **30 patients in each group**.

-Using total cost of treatment as an endpoint:

Assuming an average injection volume of 75 Units of botulinum toxin every 3 months, and assuming a cost of $12-15 per Unit, the estimated cost of a botulinum toxin A injection protocol over one year is $3,600-$4,500.

In comparison, the estimated cost of surgery (including facility fee, surgeon fee, preoperative testing and follow-up) is $8,378.[10]

Therefore, in order to demonstrate a financial superiority of surgery versus botulinum toxin, the patients would need to be follow-up for 1.9 to 2.3 years. Assuming a study follow-up of 2.5 years, and average costs of botulinum and surgery of $10,125 ± $2,000 and $8,378 ± $2,000, respectively, and assuming an alpha error of 5%, a power of 80%, the required sample size using this method is **16 patients in each group**.

-Using treatment success by trigger site as an endpoint:

According to Larson *et al*,[9] the success rates for surgery by trigger site were as follows: Frontal 83.3%, temporal 75.8%, and occipital 45.5%. In order to discern a difference between the outcomes for the two sites with the closest outcomes (frontal and temporal), and assuming a standard deviation of 10%, an alpha error of 5%, and a power of 80%, the required sample size using this method is **14 patients in each group.**

Looking at the three methods above, keeping the method yielding the highest required number of participants, and accounting for any participant drop-out, we will seek to enroll **50 patients in each group.**

c. Detailed study procedures

A neurologist will evaluate patients presenting for evaluation for treatment of migraine headaches, for confirmation of the diagnosis of migraine. The type of migraine that they suffer from will be recorded. If the diagnosis of migraine is confirmed, they will sign an informed consent form, and they will be asked to complete a daily headache diary, and keep track of their 1) daily use of medications for migraines, 2) physician visits for migraines, 3) ER visits for migraines, 4) days of work lost due to migraines, 5) other costs directly related to migraines for 2 months. They will also be asked to

complete **three questionnaires**: the **Migraine Work and Productivity Loss Questionnaire (MWPLQ)**,[11] the **Migraine Disability Assessment questionnaire (MIDAS)**[12] and the **Migraine-Specific Quality of Life questionnaire (MSQ)** at the time of enrollment.

All patients will undergo a history and physical examination, including an intranasal examination. This will include determination of the possible trigger site: frontal, temporal, occipital, and inferior turbinate/septum. The trigger site can be determined using a combination of three methods: 1) Physical examination, 2) Diagnostic botulinum toxin injection into a specific trigger point, and 3) Nerve block using a local anesthetic injected into a specific trigger point in patients having active symptoms.

The patients will be asked whether they prefer to undergo surgical decompression or a botulinum toxin protocol, and their preference will be recorded.

50 patients who prefer surgery, and who satisfy the inclusion and exclusion criteria, will be included in the study as **Group A**. The location of the trigger site(s) will be determined based on history, physical examination, a diagnostic botulinum toxin injection and/or a nerve block. If those patients are found to have a trigger site that responds to botulinum injection, they will undergo surgical decompression of their trigger site, as described in Janis *et al*[6] and Guyuron *et al*.[7] Those patients will be followed postoperatively. They will be asked to continue tracking their 1) daily use of medications for migraines, 2) physician visits for migraines, 3) ER visits for migraines, 4) days of work lost due to migraines, and 5) other costs directly related to migraines for 2 months. At 1 year, 2 years and 2.5 years postoperatively, they will be asked to fill the Migraine Work and Productivity Loss Questionnaire (MWPLQ), the Migraine Disability Assessment questionnaire (MIDAS) and the Migraine-Specific Quality of Life questionnaire (MSQ) again. They will also be examined by a board-certified neurologist at 1 year postoperatively.

A separate sample of 50 patients from the pool of patients undergoing the botulinum toxin injection protocol will be selected (Group B). Those patients will be matched to the individual patients in group A based on gender, age (in 5 year intervals), migraine severity (based on the Migraine Disability Assessment questionnaire, 5 –point intervals) and trigger site (pair-matching). For example, for a patient in Group A who is a 47 year-old woman with temporal migraines and a MIDAS severity score of 14, a patient on the botulinum injection protocol will be included in Group B is she is a 45 to 50 year old female with temporal migraines and a MIDAS severity score of 10 to 15.

The patients in group B will receive the botulinum injection protocol, and will continue to track their 1) daily use of medications for migraines, 2) physician visits for migraines, 3) ER visits for migraines, 4) days of work lost due to migraines, and 5) other costs directly related to migraines for 2 months. At 1 year, 2 years and 2.5 years after the start of the protocol, they will be asked to fill the Migraine Work and Productivity Loss Questionnaire (MWPLQ), the Migraine Disability Assessment questionnaire (MIDAS)

and the Migraine-Specific Quality of Life questionnaire (MSQ). They will also be examined by a board-certified neurologist at 1 year postoperatively.

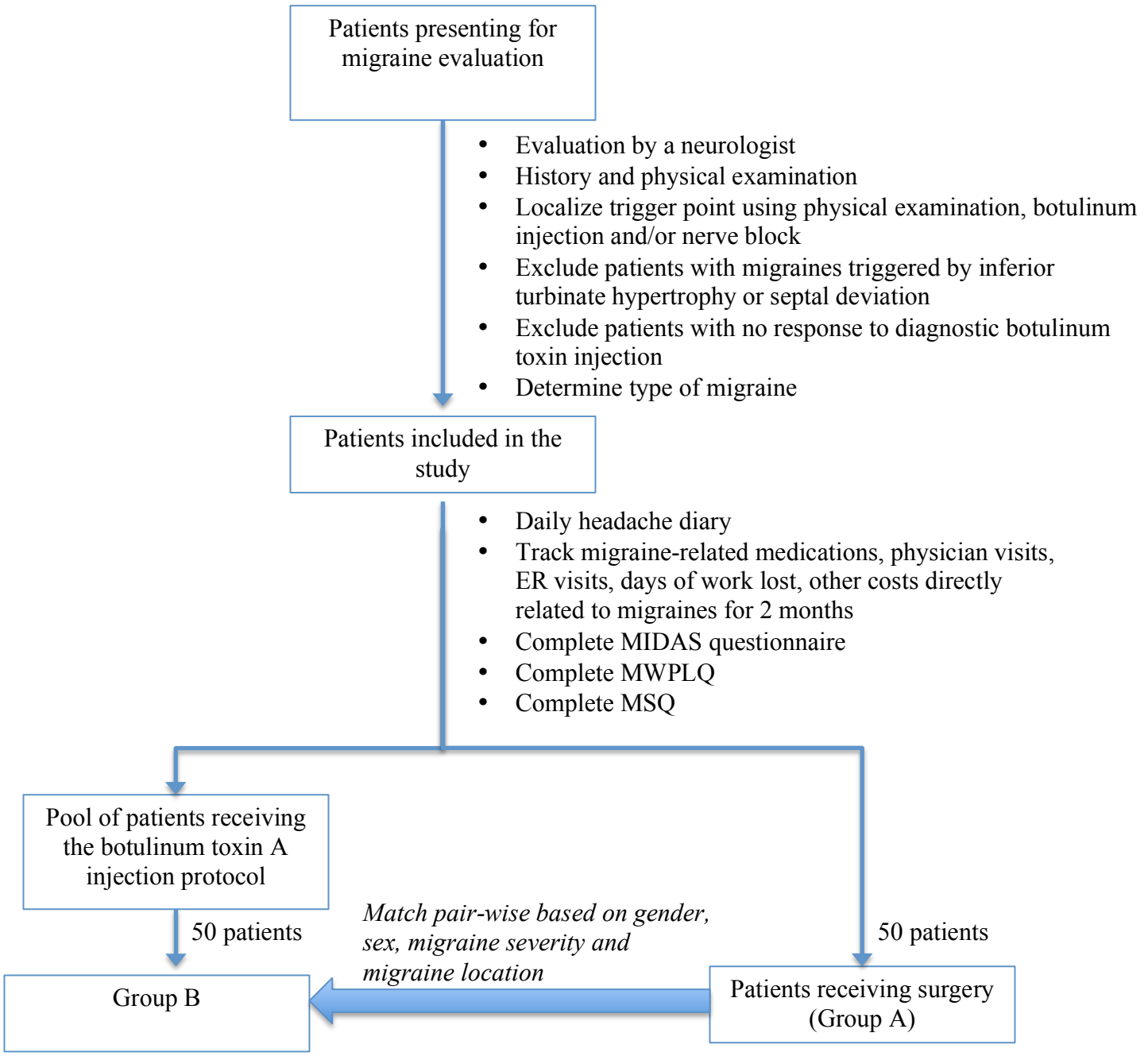
The Botox injections and the surgeries are being done as part of the routine clinical care for the patients enrolled in the study. The only procedures being done solely for research purposes are having the patients fill out the surveys and diaries.

d. Measurements

The measurements will include

1) Number of migraine headaches per 30 days
2) Cost of migraine-related medications, physician visits, ER visits
3) Cost of days of work lost due to migraine as calculated from the Migraine Work and Productivity Loss Questionnaire (MWPLQ)
4) Score on the Migraine Disability Assessment Questionnaire (MIDAS) (0-21)
5) Scores on the emotional, restrictive and preventive portions of the Migraine-Specific Quality of Life questionnaire (MSQ)

The following comparisons will be made for the above measurements:
-Within Group A, compare all measurements before surgery to 1 year, 2 years and 2.5 years after surgery, using a t-test
-Within Group B, compare all measurements before start of injection protocol to 1 year, 2 years and 2.5 years after injection protocol, using a t-test
-Compare all measurements between Group A and Group B using a paired t-test analysis


Patients presenting for migraine evaluation
Evaluation by a neurologist
History and physical examination
Localize trigger point using physical examination, botulinum injection and/or nerve block
Exclude patients with migraines triggered by inferior turbinate hypertrophy or septal deviation
Exclude patients with no response to diagnostic botulinum toxin injection
Determine type of migraine
Patients included in the study
Daily headache diary
Track migraine-related medications, physician visits, ER visits, days of work lost, other costs directly related to migraines for 2 months
Complete MIDAS questionnaire
Complete MWPLQ
Complete MSQ
Pool of patients receiving the botulinum toxin A injection protocol
50 patients
Match pair-wise based on gender, sex, migraine severity and migraine location
50 patients
Group B
Patients receiving surgery (Group A)
Follow each patient for 2.5 years from the inclusion into the study
Daily headache diary
Track migraine-related medications, physician visits, ER visits, days of work lost, other costs directly related to migraines for 2 months
Complete MIDAS, MWPLQ and MSQ at 1 year, 2 years and 2.5 years after start of injection protocol
Evaluation by a neurologist at 1 year
Follow each patient for 2.5 years from the day of surgery
Daily headache diary
Track migraine-related medications, physician visits, ER visits, days of work lost, other costs directly related to migraines for 2 months
Complete MIDAS, MWPLQ and MSQ at 1 year, 2 years and 2.5 years postop
Evaluation by a neurologist at 1 year

e. Internal validity

The study avoids confounding by virtue of the matched-pair analysis. The study avoids recall bias by having the patients fill-out the questionnaires preoperatively and postoperatively, rather than having them retrospectively assess their improvement after surgery.

Blinding is very difficult in such a study. In order to avoid experimenter bias, all assessment will be made by the patients themselves, without influence by the experimenters.

The main threat to internal validity is the possible placebo effect inherent to migraine headache treatments. This may threaten the validity of the data on differences in clinical outcomes between the two groups. It will not threaten the validity of the data on financial cost

f. External validity

Because this is a multi-center trial that includes different patient populations treated by different clinicians, this study is generalizable to the general population of patients with migraines in the United States.

g. Data analysis

Group B will be selected by matching individual participants to members of Group A based on gender, age, migraine severity and migraine location.

Within Group A, compare the measurements before surgery to 1 year, 2 years and 2.5 years after surgery, using a t-test

Within Group B, compare the measurements before the start of the injection protocol to 1 year, 2 years and 2.5 years after the start of the injection protocol, using a t-test

Compare the measurements between Group A and Group B using a paired t-test analysis

h. Bibliography

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