

**Study Design: Randomized placebo controlled trial of third occipital nerve radiofrequency neurotomy applied according to guidelines established by the International Spine Intervention Society.**

### **Background and Significance**

To be completed by the project's Principal Investigator (PI) and should include rationale for the selected study design.

### **Hypothesis**

Third occipital nerve radiofrequency neurotomy (TON RFN) is effective in reducing pain and improving function in patients who qualify for treatment based on International Spine Intervention Society guidelines.

### **Specific Aims:**

1. Determine the proportion of patients with a good response (defined as 80% or greater improvement in index headache and/or neck pain) to TON RFN at 8 weeks, and the duration of relief up to 24 months.
2. Determine the proportion of patients with a fair response (defined as 50% or greater but less than 80% improvement in headache and/or neck pain) to TON RFN at 8 weeks, and the duration of relief up to 24 months.
3. Evaluate the functional improvement observed (by Neck Disability Index (NDI)) in the entire cohort and the subgroups with fair and good response to treatment, and determine the correlation between reduction in pain and improvement in function.
4. Evaluate differences in proportion of fair and good responses in patients reporting 100% relief from dual comparative diagnostic TON blocks relative to the remaining cohort (remaining cohort, by definition will be those with at least 80% improvement but less than 100% relief from the dual comparative blocks).
5. Report adverse effects.

### **Recruitment Process**

Subjects will be recruited from the practices of the primary investigators – either in the clinic or interventional suite. If recruitment is insufficient from these sources, secondary recruitment from marketing to primary care clinics and local media is permissible.

### **Enrollment Process**

Potential candidates will be approached in clinic, or contacted by phone by the investigators or research assistant to introduce the study and proceed to a screening assessment if the potential candidate agrees. Eligibility is determined by the inclusion and exclusion criteria listed below. Qualifying volunteers will be asked to provide both written and verbal informed consent.

A power analysis has determined target enrollment of 30 patients for inclusion in the study. (Investigator to confirm, provide details of the power analysis, and adjust the target number if

needed.)

Patients may be compensated for their time and participation upon enrollment and for completion of follow-up intervals.

*Inclusion Criteria:*

- Adult patient aged 18-80 capable of understanding and providing consent in English and capable of complying with the outcome instruments used.
- Axial (non-radicular) neck pain and/or headache for at least 3 months.
- 7-day average numeric pain rating score (NPRS) for axial (non-radicular) neck pain and/or headache pain of 5/10 or greater at baseline assessment.
- Significant functional impact, defined as neck disability index (NDI) score of 30 or greater.
- Positive response to dual comparative diagnostic TON blocks, defined as reporting at least 80% relief of index pain. The patient will be given a post-procedure pain diary with instructions on how to properly complete the form. The first assessment will be the patient's recorded (written) response in the recovery room, and will be recorded 15-30 minutes after the TON block has been completed. This initial post-procedure pain score will not be verbally obtained, as the medical staff's involvement in this process will only consist of providing general instructions on how and when to complete the pain diary. In order to be considered a positive response, the patient must record at least 80% relief of index pain at the 15-30 minute post-procedure assessment, and at the 1 hour and 2 hour post-procedure assessments. (Investigator will provide an acceptable pain diary for review and approval with the grant application.)
- If possible, a research assistant or nurse should record TON distribution skin sensory changes with a pin-prick test at the 15-30 minute post-procedure assessment.

*Exclusion Criteria:*

- Radicular pain
- Myelopathy
- Unable to stay prone for at least 45 min
- History of surgery involving C2-3
- Those receiving remuneration for their pain treatment (e.g. disability, worker's compensation, auto injury in litigation or pending litigation).
- Prisoner
- Unable to read English and complete the assessment instruments
- Allergy to contrast media or local anesthetics
- Chronic widespread pain (e.g. fibromyalgia) or somatoform disorder
- Prior TON radiofrequency neurotomy
- Addictive behavior, severe clinical depression, or psychotic features
- Possible pregnancy or other reason that precludes the use of fluoroscopy

## **Outcome Instruments**

### *Baseline Only:*

- Demographics
- Time when headache and/or neck pain began
- Nature of neck pain (*i.e.* location, quality, frequency, duration)
- Nature of head pain (*i.e.* location, quality, frequency, duration)

### *Baseline & Follow-up:*

- Average 11-point numeric pain rating score (NPRS) headache (7-day average)
- Present NPRS headache
- Average NPRS neck pain (7-day average)
- Present NPRS neck pain
- EQ-5D for health-related quality of life measures
- Neck Disability Index (NDI)
- Four patient specified activities that have been impacted by pain
- Work history and current status
- Analgesic use log
- Ancillary treatment log
- Physical examination

### *Follow-up Only:*

- Global perception of change
- Adverse effects (*e.g.* postprocedural pain, ataxia, dysethesias, dizziness)
- Assessment of pin prick sensory change in TON territory at the first post-treatment visit

### *Treatment:*

- Date
- Side(s) and location(s) of treatment
- Locations of lesions
- Temperature and duration of lesions
- Sedatives used
- Type of needle used (sharp/blunt, gauge, straight/curved, active tip length)
- Saved images of final needle/electrode placement in AP and lateral views

## **Study Timeline**

### *Baseline:*

Participants who meet inclusion and exclusion criteria will be enrolled into the study after consenting to and before receiving a TON RFN. The baseline examination and all baseline

questionnaires will be completed within 2 weeks before the procedure.

*Follow-up:*

Routine scheduled follow-up will occur at 2 weeks (+/- 1 week), 8 weeks (+/- 2 weeks), 6 months (+/- 2 weeks), 12 months (+/- 1 month), and 24 months (+/- 1 month), at which times all follow-up measures will be obtained.

The 8-week follow-up will serve as the time point for the primary outcome analysis of the randomized trial and an intention to treat analysis used to evaluate for differences in outcomes between active treatment and controls. The 8-week time point provides a reasonable timeframe to evaluate the clinical effects of the TON RFN while also providing a humane timeframe for crossover to active treatment in those randomized to placebo. All subsequent follow-up periods are intended to evaluate long-term clinical outcomes of TON RFN and will be evaluated with an as treated analysis.

The study start date and the outcome assessment timeline will begin from the date of the participant's initial TON RFN or placebo treatment. During the first 8 weeks from this start date, a participant must remain blinded to assigned treatment. After 8 weeks, patients who have failed treatment (not meeting criteria for a fair or good response as described above) can be unblinded. Those who received active treatment will be considered treatment failures, by definition, and continue on the regular follow-up schedule. Those treated by placebo may opt to crossover to active treatment, and in so doing will begin a new 2-year follow-up for the active treatment.

This study is intended to monitor outcomes for 24 months following TON RFN. Some patients reporting relief at the 8-week follow-up may experience a return of symptoms after this. All patients reporting relief at the 8-week follow-up will be instructed to contact their physician if and when pain returns to arrange for a repeat treatment. This can occur at any time following the 8-week follow-up, including the regularly scheduled follow-up intervals or anytime between. Repeating the TON RFN beyond the 8-week follow-up does not reset the follow-up schedule, and does not indicate a treatment failure (which are determined by the pre-selected thresholds for the measured pain and disability outcomes).

**Study Protocol**

*Procedures:*

All TON (diagnostic) blocks and radiofrequency neurotomy procedures, including the needle position, will be performed according to International Spine Intervention Society guidelines. As is the standard of care, selection of patients for the diagnostic TON blocks will be determined by the treating physician based on the overall clinical picture including the location of pain, pain referral patterns, and imaging findings. The principal investigator will provide full procedural details, including a list of equipment to be used, needle type, lesion number, locations, and parameters.

The principal investigator should outline all details of the sham procedure protocol, including that needle and electrode final placement will remain posterior to the pillar.

*Group Assignments:*

Patients are randomly assigned to the active treatment or control groups. Each group will have at least 15 patients.

Subjects who achieved 50% or more relief of their usual pain at the 8-week follow-up and who subsequently experience a recurrence of their usual pain will be offered a repeat procedure.

Duration of relief from the index TON RFN will be considered the time from the provision of the TON RFN procedure until the subject returned to 50% of their pre-treatment level of pain as reported during scheduled follow-up, or when a repeat TON RFN is requested and performed, or 24 months if greater than 50% relief persists to the final scheduled follow-up.

*Crossover:*

Any time after the 8-week follow-up, any participant not obtaining adequate pain relief can ask to be unblinded, and if in the control group can opt to crossover to active treatment. In doing so, a new 2-year follow-up will begin for this patient who is now placed in the active treatment group for the long-term as treated outcomes analysis.

*Co-interventions:*

Patients are allowed to receive usual care, including co-interventions, as deemed necessary by the treating physician. Any treatments related to the participant's headache or neck pain will be reported on the ancillary treatment log.

*Primary Outcomes:*

The primary outcome for the randomized trial is "treatment response" at the 8-week follow-up.

Treatment response will be categorically evaluated as "good" ( $\geq 80\%$  relief of headache and/or neck pain by NPRS), "fair" ( $\geq 50\%$  but less than  $80\%$  relief of headache and/or neck pain by NPRS) and "failed" (less than  $50\%$  relief of headache and/or neck pain by NPRS). Participants rate headache pain and neck pain separately. For each participant, the greater of the two at the baseline measurement will be identified as the pain measure to use in the primary outcomes analysis.

*Secondary Outcomes:*

1. Duration of treatment response up to 24 months
2. Disability outcomes (NDI)
3. Health-related quality of life (EQ-5D)
4. Four patient specified activities that have been impacted by pain
5. Health-care utilization for neck pain
6. Work status

*Blinding:*

This is a double-blinded study. Patients will remain blinded to their group assignments throughout the study unless they meet criteria for crossover treatment. A blinded independent assessor will obtain and measure outcomes as the treating physician cannot be blinded. The treating physician will receive the randomization assignment and implement either active or sham treatment. The treating physician's performance of the active and sham treatments will differ only by the final location of the needles and electrodes, and the application of radiofrequency energy. Otherwise, all other aspects of the procedures will be identical including equipment sounds and procedure durations. Radiofrequency energy will be applied to those in the active treatment group, and not to those in the sham group, under the control of the treating physician and without the independent assessor's knowledge.

### **Data Management**

Data will be collected on standardized case report forms and entered into a HIPPA-compliant electronic database (*e.g.* Microsoft Access) that provides an appropriate interface with a robust statistical package (*e.g.* SPSS). All study-related hard copy materials will be stored in locked file cabinets.

### **Analysis**

As per the study protocol, participants rate headache pain and neck pain separately. For each participant, the greater of the two at the baseline measurement will be identified as the pain measure to use in the primary outcomes analysis.

Results of the randomized controlled trial will be determined by an analysis of categorical data from the 8-week follow-up. At 8-week follow-up, prior to allowing crossover, overall treatment response rates (in the previously defined categories of failed, fair, or good) will be calculated for both active treatment and control groups using an intention to treat analysis. For time periods beyond 8-weeks, intention to treat and as treated analyses will be performed with primary reporting based on the as treated analysis to assess the long-term effectiveness of active treatment.

Subgroup analyses will be performed to assess treatment response and long-term effectiveness in patients reporting 100% relief from TON blocks as compared with those reporting between 80-99% relief, and comparing those with greater headache pain to those with greater neck pain. Data will also be examined to identify any factors tied to treatment success and need for repeat treatment. For instance, the presence of pin-prick test sensory changes following diagnostic TON nerve blocks can be examined to determine its predictive value for successful clinical response to subsequent radiofrequency neurotomy.

Secondary outcomes will be similarly evaluated. The four patient-specified activities that have been impacted by pain will be categorically analyzed as either resolved or not. For NDI and EQ-5D, the proportions of those achieving and not achieving the established minimal clinically important differences (MCID) will be determined and compared between the active treatment

and control groups at the 8-week follow-up. For long-term analysis of treatment effectiveness, an as treated analysis will determine the proportion of patients exceeding these response thresholds. In addition to these categorical outcomes, changes in group means scores will be measured and compared, as will health care resource utilization and work status. Correlation between reduction in pain and improvement in function will be evaluated with a regression analysis of changes from baseline to 8-week follow-up. Finally, all adverse events will be recorded and reported for both the active treatment and control groups.