

**Study Design: Randomized placebo controlled trial of cervical medial branch radiofrequency neurotomy applied according to guidelines established by the International Spine Intervention Society (ISIS)**

**Background and Significance**

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

**Hypothesis**

Cervical medial branch radiofrequency neurotomy (CMB RFN) is effective in reducing pain and improving function based on patients who meet ISIS guidelines.

**Specific Aims:**

1. Determine the proportion of patients with a good response (defined as 80% or greater improvement in index pain) to CMB 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 neck pain) to CMB RFN at 8 weeks, and the duration of relief up to 24 months.
3. Evaluate the functional improvement observed (by 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 cervical medial branch 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 evaluation 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 for at least 3 months.
- 7-day average numeric pain rating score (NPRS) for neck pain of 5/10 or greater at baseline evaluation.
- Significant functional impact, defined as neck disability index (NDI) score of 30 or greater.
- Positive response to dual comparative diagnostic medial branch blocks, defined as reporting at least 80% relief of index pain. The patient will be given a post-procedure pain diary with instruction 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 medial branch 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 applications.)

*Exclusion Criteria:*

- Those receiving remuneration for their pain treatment (*e.g.* disability, worker's compensation, auto injury in litigation or pending litigation).
- The patient is incarcerated.
- Those unable to read English and complete the assessment instruments.
- Allergy to contrast media or local anesthetics.
- Chronic widespread pain or somatoform disorder (*e.g.* fibromyalgia).
- Prior cervical medial branch 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

- Duration of neck pain
- Nature of pain (*i.e.* bilateral symmetrical, unilateral)

*Baseline & Follow-up:*

- Average NPRS neck pain (7-day average)
- Present NPRS
- EQ-5D
- NDI
- Four patient specified activities that have been impacted by pain
- Work history and current status
- Analgesic use log
- Ancillary treatment log
- Physical examination
- Presence/absence of headache

*Follow-up Only:*

- Global perception of change
- Adverse effects (*e.g.* postprocedural pain, numbness/paresthesias)

*Treatment:*

- Date
- Side(s) and location(s) of treatment
- Temperature and duration of lesions
- Sedatives used
- Type of needle used (sharp/blunt, gauge, straight/curved, active tip length)

**Study Timeline**

*Baseline:*

Participants who meet inclusion and exclusion criteria will be enrolled into the study after consenting to and before receiving a CMB 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 CMB 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 CMB 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 CMB 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 CMB 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 CMB RFN beyond the 8-week follow-up does not reset the follow-up schedule.

## **Study Protocol**

### *Procedures:*

All medial branch blocks and radiofrequency neurotomy procedures will be performed according to ISIS guidelines, with the radiofrequency neurotomies and sham procedures performed at the same levels identified by the diagnostic medial branch blocks. All levels that were determined to be positive by the diagnostic procedures will be treated. Levels selected for diagnostic procedures 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 equipment to be used, needle type, lesion number and parameters.

### *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 will be considered the time from the provision of the CMB 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 CMB RFN is requested and performed.

*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 spine condition 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 neck pain by NPRS), fair ( $\geq 50\%$  but less than 80% relief of neck pain by NPRS) and failed (less than 50% relief of neck pain by NPRS).

*Secondary Outcomes:*

1. Disability (NDI)
2. Health-related quality of life (EQ-5D)
3. Four patient specified activities that have been impacted by pain
4. Health-care utilization for neck pain
5. 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. The treating physician, who is also the outcomes assessor, will also remain blinded. A trained study nurse or assistant not involved in the patient's care will receive the randomization assignment and implement either active or sham treatment. The treating physician's performance of the active and sham treatments will be identical. 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 trained study nurse or assistant and without the treating physician's knowledge. Otherwise, all other aspects of the procedures will be identical including needle and electrode placements, visual indications, equipment sounds, and procedure durations.

**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**

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 cervical medial branch blocks as compared with those reporting between 80-99% relief. Data will also be examined to identify any factors tied to treatment success and need for repeat treatment.

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.