**RANDOMIZED CONTROLLED TRIAL OF LUMBAR RADIOFREQUENCY NEUROTOMY**

**Study Design**
Randomized placebo-controlled trial of lumbar medial branch radiofrequency neurotomy applied according to guidelines established by the Spine Intervention Society (SIS)

**Background and Significance**
To be completed by the project's Principal Investigator (PI).

**Hypothesis**
Lumbar medial branch radiofrequency neurotomy (LMB RFN) is effective in reducing low back pain originating from the zygapophysial joints. A secondary outcome is improvement in function.

*Specific Aims:*

1. Determine the proportion of patients with a good response (defined as 80% or greater improvement in index pain) to LMB RFN at 12 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 pain) to LMB RFN at 12 weeks, and the duration of relief up to 24 months.
3. Evaluate the functional improvement observed 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. Report adverse effects.

**Recruitment Process**
Subjects will be recruited from the practices of the primary investigators, i.e., clinic. If recruitment is insufficient from these sources, secondary recruitment from marketing to primary care clinics and local media is permissible. Co-investigators from international clinical sites are encouraged.

Investigators should record the total number of patients screened for potential enrollment in addition to the total number of patients enrolled and randomized. Patients who decline randomization may be enrolled as a separate cohort to compare their outcomes at the same time points as the study's enrolled subjects. A central study coordinator is recommended for the coordination and oversight of recruitment across clinical sites.

**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.

**Sample Size Estimation:**
A power calculation using survival analysis was performed assuming a 60% success rate (based on MacVicar *et al.* Lumbar medial branch radiofrequency neurotomy in New Zealand. *Pain Medicine*, 2013; 14(5):639-45) for the treatment group and 20% success of the placebo group, alpha 0.05, beta 0.2, ratio

= 1 (1:1 treatment vs. control). This resulted in a requirement of 25 patients in the treatment group and 25 in the control group. Assuming a 15% loss to follow up, 29 subjects would be required in each group.

For comparison, a power analysis was also performed using categorical proportions, using a ratio = 1 (1:1 treatment vs. control), 80% power, with a chi-squared test at a level of significance of 0.05, assuming the proportion of patients achieving success in the treatment group is 0.60 (60%) and 0.2 (20%) in the control group. This results in the requirement of 23 patients in both the treatment group and the control group. Assuming a 15% loss to follow-up, 27 subjects would be required in each group. Using an n of 27 in our proposed treatment group with 60% success rate, the 95% confidence intervals (CI) are 41-76%. Using an n of 27 for the placebo group and 20% success rate, the 95% CI are 8-37%. In this conservative scenario, the confidence intervals do not overlap.

The investigators will include 58 patients total, 29 in the treatment arm and 29 in the control arm as survival analysis (primary) and categorical analysis (secondary) will be performed for data analysis.

Investigator to confirm the study's target enrollment number and provide details in support of the target effect size. Investigator to confirm that the co-investigators at any additional study sites can achieve the effect size necessary to yield the target enrollment number in a reasonable amount of time.

Patients may be compensated for their time and participation upon enrollment and for completion of follow-up intervals. Funding would be limited to compensation to study sites based on enrolled patients only.

*Inclusion Criteria:*

- Adult patient aged ≥ 40 capable of understanding and providing consent in English and capable of complying with the outcome instruments used.
- Axial (non-radicular) back pain for at least 6 months that did not respond to conventional treatment such as physical therapy. The pain can be unilateral or bilateral. The pain can also include referred lower limb pain.
- 7-day worst numeric pain rating score (NPRS) for back pain of 5/10 or greater at baseline evaluation.
- Positive responses to dual comparative diagnostic medial branch blocks using bupivacaine and lidocaine. This is defined as at least 80% relief of the index pain following each block. The SIS criteria specify that the different anesthetic blocks of the zygapophysial joint(s) must be performed on separate days. The blocks are administered in a double-blind fashion so that neither the subject nor the independent assessor is aware of the local anesthetic used.

The investigator will provide an acceptable pain diary to the patient (NPRS). The severity of pain is recorded at baseline and subsequently at 30 minutes and one hour. Thereafter, the patient must record the level of pain on an hourly basis for six hours.

In order to qualify as a positive block, the response from the bupivacaine must last longer than the lidocaine. While the patient is in the recovery suite, the independent assessor evaluates him/her with a simple physical examination at 15 minutes and 30 minutes after the procedure and records the level of pain on a NPRS and whether there are any adverse side effects. The patient is discharged from the recovery suite after 30 minutes, provided that there are no adverse effects that require more attention.

The pain relief can include relief in a specified area, e.g. the pain relief can be relief on the right side only. It does not preclude a different diagnosis at a different site, e.g. upper lumbar area.

*Exclusion Criteria:*

- Receiving remuneration for pain treatment (e.g. disability, worker's compensation, auto injury in litigation or pending litigation)
- History of prior lumbar spine surgery
- Spondylolisthesis at affected or adjacent level
- BMI >35
- Incarceration
- 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 lumbar medial branch radiofrequency neurotomy
- Addictive behavior, severe clinical depression (preferably documented with an outcome scale), or psychotic features
- Possible pregnancy or other reason that precludes the use of fluoroscopy
- Patients on chronic daily opiates

**Outcome Instruments**

*Baseline Only:*

- NIH Minimal Dataset, Task Force on Research Standards for Chronic Low-Back Pain
    - Demographics
    - Duration of back pain
- Nature of pain (i.e. bilateral, symmetrical, unilateral)

*Baseline & Follow-up:*

- NIH Minimal Dataset, Task Force on Research Standards for Chronic Low-Back Pain
    - Average NPRS back pain (7-day average)
    - Physical function
    - Depression
    - Sleep disturbance
    - Pain interference with activity
    - Opioid use
    - Employment status
- Analgesic use log
- Ancillary treatment log
- Current NPRS
- EQ-5D
    - Quality of life

*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. The preference is for 80$^{o}$C for 120 seconds, including a ramp up time of 30 seconds.
- Sedatives used
- A 16-18-gauge needle with a 10 mm active tip shall be utilized. Needle length shall be sufficiently long to perform the RFN according to SIS guidelines. Lesioning shall be formed in accordance with the *International Spine Intervention Society's 2nd Edition Practice Guidelines*.

**Study Timeline**

*Baseline:*

Participants who meet inclusion and exclusion criteria will be enrolled into the study after consenting to and before receiving a LMB 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 4 weeks (+/- 1 week), 12 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 12-week follow-up will serve as the time point for the primary outcome analysis of the randomized trial and an intention-to-treat analysis will be used to evaluate for differences in outcomes between active treatment and controls. The 12-week time point provides a reasonable timeframe to evaluate the clinical effects of the LMB 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 LMB RFN and will be evaluated with an as-treated analysis.

The study start date and the outcome assessment timeline will begin at the date of the participant's initial LMB RFN or placebo treatment. During the first 12 weeks from this start date, a participant must remain blinded to assigned treatment. After 12 weeks, patients who have failed to respond to treatment (not meeting criteria for a fair or good response, as described above) may be unblinded. Those who received active treatment but failed to achieve pre-determined responses will be considered treatment failures by definition and continue on the regular follow-up schedule. Those treated by placebo may opt to cross over 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 LMB RFN. Some patients reporting relief at the 12-week follow-up may experience a return of symptoms afterwards. All patients reporting relief at the 12-week follow-up will be instructed to contact their physician if and when the patient experiences a treatment effect that diminishes by > 50%. This can occur at any time following the 12-week follow-up, including the regularly scheduled follow-up intervals. Repeating the LMB RFN beyond the 12-week follow-up does not reset the follow-up schedule. Patients are also free to choose alternative therapies beyond 12 weeks, such as surgical intervention. Patients may also develop new low back pain that is different from what is being evaluated, which will be noted. (Note: Repeat RFN may not be covered by many payers if the first does not provide 6 months of relief. Protocol timeframe may require adjustment based on regional payer policy or budget may need to include alternate source of funding for repeat RFNs prior to 6 months.)

**Study Protocol**

*Procedures:*

All medial branch blocks and radiofrequency neurotomy procedures will be performed according to SIS guidelines, with the radiofrequency neurotomies and sham procedures performed at the same levels identified by the two 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.

Prior to selection as an investigator in the study, participating physicians will be required to submit to a practice audit, presenting clinical notes and images that document previous experience in performing blocks in accordance with SIS guidelines.

The principal investigator will provide full procedural details, including a list of equipment to be used, needle length, lesion number, and parameters.

The physician performing the procedure and the assessor must be blinded as to the whether the treatment is active or placebo. The placebo treatment is performed in the same manner as the active treatment. The temperature of the active treatment is $80^{o}$ Celsius and the temperature for placebo treatment is $37^{o}$ Celsius.

Protocol should include a quality monitoring board tasked with reviewing clinical notes documenting inclusion/exclusion criteria and appropriate technique, as well as procedural images of final needle placement in AP and lateral views for every RFN procedure for the purpose of quality control. Options for the quality monitoring board include a group of SIS Research Division and/or Board members on a volunteer basis or a group of approved SIS members. Subjects with sub-optimal images shall be withdrawn from the trial as protocol violations.

*Group Assignments:*

Patients are randomly assigned by a computerized random number generator program to the active treatment or control groups. The principal investigator should further describe the randomization process. The active group will receive a radiofrequency denervation procedure. The control group will receive a sham procedure.

Subjects who achieved 50% or more relief of their usual pain at the 12-week follow-up and who subsequently incur a treatment effect that diminishes by > 50% will be offered a repeat procedure.

Duration of relief will be considered the time from the provision of the LMB 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 LMB RFN is requested and performed.

*Crossover:*

Any time after the 12-week follow-up, any participant not obtaining adequate pain relief can ask to be unblinded, and, if in the control group, can opt to cross over 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 12-week follow-up.

Treatment response will be categorically evaluated as "good" (≥ 80% relief of back pain by NPRS), "fair" (≥ 50% but less than 80% relief of back pain by NPRS), and "failed" (less than 50% relief of back pain by NPRS). Categorical success will be defined as "good" or "fair" relief. Subjects will be considered failure if they do not meet this threshold of improvement on NPRS, if they request cross-over to the other group, or if they have undergone surgery.

*Secondary Outcomes:*
1. Physical function
2. Health-related quality of life
3. Pain interference with activity
4. Health-care utilization for back pain
5. Work status
6. Likelihood of repeat RF reinstating relief

*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 will also remain blinded. In order to provide an unbiased assessment, the treating physician must be different from the outcome assessor. 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. Investigator may consider implementing a questionnaire of the treating physician immediately following the procedure to determine the success of the blinding.

The same outcomes will be tracked in the cohort that did not agree to be randomized but did agree to have their outcomes tracked.

**Data Management**
Data will be collected on standardized case report forms and entered into a HIPAA-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**

*Primary Outcomes Analysis:*

Survival analysis will be used to compare the duration of success between the treatment and control groups. The equality of the curves between the treatment and control groups will be determined using the Mantel-Haenszel test.

Categorical success will be defined as "good" or "fair" relief. Subjects will be considered a failure if they do not meet this improvement threshold of on NPRS or if they have undergone surgery. Patients will remain blinded and may not request cross-over until 12 weeks. If a patient in the sham group requests cross-over, they will be considered a failure. If a patient in the treatment group is categorized as a success at the 12-week mark but then has increased pain such that the treatment effect achieved at the 12-week mark diminishes by $\geq$50%, they will be offered a repeat procedure but be considered a failure at that time point and beyond. If the repeat procedure reinstates the relief to > 50% baseline then the subject will be considered a categorical success for reinstatement of relief only.

Subjects who have crossed over to the treatment group will be considered failures for the purposes of survival analysis. They will be included in an intent-to-treat analysis and a per protocol analysis, with presentation of both results. A sensitivity test comparing the two analyses is desirable if the investigators have expertise or access to statistical support.

*Secondary Outcomes Analysis:*

Categorical analysis and descriptive measures will be used for secondary outcome analysis of NIH Minimal Dataset elements. These will include global impression of pain, patient-specified functional outcome scale activity restoration, pain interference, medication use, other healthcare utilization, and work status.

Additional secondary outcome analysis for success will be based upon minimal clinically important difference (MCID) of both pain and function: improvement of 2 points of NRS and 30% points improvement in function on items 16-19 of the NIH Minimal Dataset at all follow-ups.

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 mean 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 12-week follow-up.

The proportion of patients who had success reinstated from repeat RF will be compared to those who had an unsuccessful reinstatement of relief using the same criteria for success as well as for duration.

The proportion of patients from the study site(s) who were eligible for the study but declined to participate may also be analyzed as an open cohort for comparison to study subjects as well as to document the implementation challenges associated with randomized controlled trials in this field. At a minimum, the number of patients who were eligible but did not participate should be noted.

Finally, all adverse events will be recorded and reported for both the active treatment and control groups.