Protocol Title: Threshold Response of Lumbar Selective Nerve Root Block in Predicting Good Outcome Following Lumbar Foraminotomy

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Problem

Lower extremity radiculopathy due to lumbar degenerative disease is a common presenting complaint. The prevalence is reported to be 3-5% of the US population[24] while the annual cost to care for patients with lumbar degenerative disease is estimated to be $50 billion[1]. Although lumbar radiculopathy patients often present with diffuse degenerative disease, the specific nerve and/or nerve foramen causing the presenting symptoms is often unclear. This diagnostic uncertainty can be addressed with a selective nerve root block (SNRB). Surgical decision-making is then based on the patient's positive or negative response to the SNRB. Despite the widespread use of SNRB to localize the source of lumbar radiculopathy, prior studies of the positive and negative predictive value of SNRB in this patient population found mixed results. Possible explanations for this heterogeneity include a lack of a standardized approach to performance of a SNRB and difficulty performing an accurate injection. Furthermore, there is no standardization for what constitutes a positive injection response and no objective measures exist to determine SNRB effectiveness.

It is overly simplistic to rely on a dichotomous response to a SNRB, i.e., positive or negative. There is likely a threshold of response based on the degree of pain improvement, duration of improvement and/or improvement on an objective test such as a walking test. **The proposed study will be the first to prospectively assess the threshold of patient response to SNRB when predicting objective outcomes.** Our study seeks to assess what degree or length of improvement in subjective pain and objective walking predicts an optimal outcome following lumbar foraminotomy. The results of this pilot study may be used to plan a larger multicenter prospective study. As the US health care system continues to transition toward value-based care, quantifying the clinical efficacy of common interventions such as SNRB become increasingly important. The results of the proposed pilot study and the future multi-center trial will advance lumbar spine care in an environment of value-based care.

Specific Aims and Hypothesis

Diagnostic selective nerve root blocks (SNRBs) are often utilized in the management of lumbar degenerative disease. It is estimated that 2 million spinal injections are performed annually in Medicare patients alone. Each injection costs approximately $2000, resulting in an annual expenditure of $4 billion. The sensitivity and specificity of SNRB have been previously reported in several studies with the sensitivity ranging from 9-100% and specificity ranging from 24-96% depending on the reference standard used[6]. The data regarding diagnostic accuracy are largely inconclusive with the reasons for the observed heterogeneity including inconsistencies in procedure and approach for administering the nerve block, lack of a standard evaluation of nerve block response, relative dearth of up-to-date studies (older studies may have out of date practices), small sample sizes, study design (mostly retrospective), and

operator variances. Another important reason for variance in previously published results is the lack of a standard for a threshold level of nerve block that constitutes a positive diagnostic SNRB. The proposed study will address all of these problems by quantifying the predictive value of diagnostic SNRBs in patients who present with lumbar foraminal stenosis and radiculopathy. The proposed study will identify the threshold response level that optimizes this predictive power. Specifically, the proposed study will address the question of whether there is a degree or length of response to SNRB, which predicts an excellent surgical outcome. **We hypothesize that diagnostic SNRBs, when performed correctly, are useful in localizing the level of involvement in LSS and improve the accuracy and efficacy of surgical intervention.** Use of diagnostic SNRBs will thus be used to clarify the clinical picture, giving the surgeon the information to make the right decision to operate or not, and, in the case of operation, predicting the optimal level (s) for surgical intervention. In addition, **we plan to identify and fully characterize a standard threshold level and time of nerve block response that will optimize the accuracy, specificity, and sensitivity of SNRB in predicting surgical outcomes.**

Aim 1: Prospectively determine the positive and negative predictive value of SNRB in the surgical treatment of lumbar foraminal stenosis. Prior to a single level foraminotomy for lumbar foraminal stenosis patients will undergo SNRB of the suspected nerve root. All enrolled patients will proceed to surgery despite the response to injection. All injections will be performed in a standard format-utilizing anesthetic only and under fluoroscopic guidance. All patients will complete an ambulation assessment immediately before and following the injection. Distance and time will be recorded. All injection patients will be called within 48 hours of the injection to determine response to the injection and recorded as Pre- and Post injection VAS leg as well as length of time of the response recorded in minutes. Patients will be seen at 6 weeks, 3 months and 12 months following surgery and outcome measured by VAS-leg, Oswestry Disability Index (ODI), Pain Disability Questionnaire (PDQ) and EQ-5D.

Aim 2: Determine the threshold of positive predictive response. The relationship between degree of pain improvement following SNRB and outcomes following surgery is currently unknown. Each patient will therefore report their change in leg pain before and after injection as well as the length of time of improvement. These data will be used to determine the optimal improvement in leg pain and duration of improvement, which predicts a statistical and meaningful improvement in leg pain following foramintomy.

Background and significance

Lumbar radiculopathy in the setting of degenerative disease is a common presenting symptom; its prevalence is estimated to be 2-5% of the US population. Although patients typically present with pain associated with one or multiple nerve roots, their MRI may demonstrate multi-level foraminal and/or

canal stenosis. Moreover, these degenerative findings seen on imaging are common in asymptomatic people. Several studies have found no correlation between MRI findings and clinical symptoms[4, 16, 17, 25]. Others have shown that MRI evidence of stenosis increases with age despite absence of symptoms, noting that almost 20% of individuals >60 years of age and up to 80% of those >70 years of age have evidence of stenosis without clinical symptoms[3, 20].

In many cases the combination of patient history, physical exam and MRI findings may localize the source of radicular pain. In others, the findings are equivocal and a selective nerve block may be used as a diagnostic tool. Studies on the ability of SNRB to predict outcomes of spinal surgeries have been largely inconclusive. The diagnostic yield is reported to vary from 30-90%[7, 10, 21]. This variability has been attributed to several factors including: 1) the retrospective nature and sample size of existing studies, 2) variability in SNRB methods, and 3) a lack of standard for a positive response to the nerve block.

Prior studies have reported both the positive and negative predictive value of SNRBs[5,6,11,19,28]. Despite numerous reports, deficiencies in the literature are noteworthy. Most studies assessing the ability of SNRB to predict outcomes following decompression have been retrospective in nature, lack a comparison group, and report relatively small sample sizes, ranging from 39 to 105 patients.

Sasso and colleagues retrospectively reviewed their experience with selective nerve blocks in predicting surgical outcome for lumbar and cervical radiculopathy. The authors reviewed 101 patients all, which underwent cervical or lumbar decompression. The injection technique was standardized for both the cervical and lumbar regions. A positive injection was determined if there was an immediate >95% relief of pain and VAS score of 0-1. The overall predictive value of SNRB was 91% while the negative predictive value was 40%[21]. Williams and Germon recently reported on their experience with SNRB in 100 consecutive patients. This retrospective review included patients who presented with diagnostic uncertainty based on history, physical exam and imaging as to whether nerve root compression was responsible for their symptoms. All patients had imaging demonstration of either foraminal or lateral recess stenosis. All patients underwent a standardized injection performed by the same operator. A standardized approach to a positive or negative injection was utilized. Specifically, the injection to be effective result in 1) initial reproduction of the patient's typical radicular pain, 2) an initial radiculogram, 3) an appropriate motor and sensory disturbance immediately after blockade and 4) and whether good pain relief during activity was present during presence of blockade. In patients who's symptoms did not improve 3 months after surgery, an MRI was ordered. Fifty-one patients underwent decompression surgery after a successful SNRB; 41 patients had a good outcome after surgery, while 10 did not. Nine patients who did not have relief of their pain still underwent decompression surgery; 6 of these patients had relief of their symptoms, 2 did not improve and one was lost to follow-up. The positive predictive value was found to be 80.4%; while the

negative predictive value was 22.2%. The resultant sensitivity was 85.4% and specificity 16.7%[26].

Both Sasso et al. and Williams and Germon studies are limited by their retrospective design. Bias regarding patients chosen for surgery, type of surgery performed and ultimate outcome cannot be minimized or mitigated. Patients included were not homogeneous, especially in Sasso et al, where cervical patients were included. Validated patient reported outcome measures were not utilized, which negatively impacts the true definition of outcome following surgery and overall predictive value of SRNB. Most importantly, the threshold for a positive response was determined and set *a priori* in both studies. A dichotomous positive or negative response to injection was utilized and is likely overly simplistic. As stated by the authors, the threshold for a positive response may have been set too high and this could have explained the low negative predictive value of SNRB reported. Lastly, the sample size in both studies was too small to make subgroup analysis and determine which aspects of the response to the SNRB predict a good surgical outcome.

There is currently no agreed upon gold standard against which to make comparisons of accuracy of SNRB. Some have defined accuracy based on demonstration of epidural spread of contrast along the nerve of interest[27], anatomic studies[15], changes in physiology[22], or compared to EMG or myelography[10]. Moreover, there is no agreed upon standardized needle placement for SNRB. The needle may be placed classically at the superior anterior foramen, alternatively, the needle may be placed in Kambin's triangle. Both target the nerve in the foramen, but at differing anatomic positions. An injection in either place should block the desired nerve, but in differing anatomic locations and potentially resulting in a varying diagnostic response. Many consider a transforaminal epidural steroid injection diagnostic, yet this injection involves epidural placement of drug and steroid and thus is not diagnostic. Lastly, there is no standard as to what medication or cocktail of medication and volume should be injected. Differing volumes and concentration of anesthetic injected will obviously have a variable impact on diagnostic accuracy.

SNRB are technically difficult and the ability to selectively anesthetize a single nerve root has been questioned. The more recent studies attempt to circumvent this issue artificially by application of contemporaneous imaging to confirm SNRB placement in the correct location[26, 28]. Evidence suggests that compression of the dorsal root ganglion is more predictive of radicular symptoms as compared to a more central region of compression[8, 18]. Ideally, the target of "block" should be the DRG. There is known variation in the location of DRG in foramen, it may be located intraforaminally, extraforaminally, or intraspinally[15]. In order to account for this, some studies have used electrostimulation in addition to fluoroscopy[27]. This variability has impact on the diagnostic yield of SNRB.

Another issue with SNRB is the lack of consensus on what constitutes a "positive" response. Some use a dichotomous approach with any improvement in pain used as a positive response, while others document an *a priori* level of pain improvement as a determination of "positive". Some use an arbitrary cut-off in pain reduction; 50%, 80% or a two-point reduction in the visual analog pain scale[22]. If the cut-off is not met, the nerve is determined to not be the pain generator. This arbitrary approach may have a significant impact on determination of diagnostic accuracy. Patient expectations and placebo may also have an impact on diagnostic results. The impact is unknown but must be minimized or at least realized when utilizing SNRB. "Blinding" the patient to the procedure and a standardized informed consent and pre- and intraprocedural flow should minimize impact.

The view that a dichotomous response (positive vs. negative) to SNRB is overly simplistic. It is likely that there is a threshold of response, which predicts improving outcomes. It may be that as the degree of pain or functional improvement following injection will have a greater predictive value. Moreover, improvement on some aspects of the injection but not all may still predict a good outcome (i.e., motor and sensory changes in the nerve of interest but no significant improvement in pain). Knowledge of such a diagnostic threshold will help plan ultimate surgical or non-surgical treatment.

The true positive and negative predictive value of SNRB can only be determined in a prospective randomized controlled trial. A standardized approach to patient selection in a homogenous cohort utilizing a standard injection technique and outcome measure is required. Moreover, it is likely that an objective functional assessment vs. simple pain assessment should be utilized in determining a "positive" response. Recent studies have shown that functional assessment by walk test can be a quick and cost efficient way to assess severity of disability in patients. Walk tests are an improvement on inherently biased questionnaires that are subject to a patient's ability to recall. A variety of walk tests have been used in the past to assess functionality including a 10-meter walk test, 30-meter walk test, 6 minute walk test, and exercise treadmill test. The 10-meter walk test is less applicable in this setting since it is largely a test of speed. The 30-meter walk test, 6 minute walk test, and exercise treadmill tests are relatively similar. The most detailed studies have been done on the 30-meter walk test in assessing lower extremity functional status in cervical myelopathy and are applicable in this setting [2, 12]. With this test, patients are asked to walk 30 meters. Time and count of cadence to walk 30 meters are recorded. The onset of pain, as well as distance and time until pain occurs are recorded. Limitations due to pain is assessed by time taken to complete test as well as cadence count.

Our belief is that SNRB, as measured by the change in pain and objective functional ability, can solicit crucial information regarding a patient's clinical picture and can predict a patient's outcome post-surgery. By using the walk test

as an objective functional assessment, we hope to better standardize the threshold for a positive response to SNRB.

In summary, SNRB, despite utilized frequently in the diagnostic work-up with patients with lumbar radiculopathy, vary widely in their sensitivity and specificity. The reasons, as outlined above, are multifactorial. The proposed study aims to minimize the known limitations of these injections and prospectively define their positive and negative predictive value in a homogenous group of patients undergoing surgery for lumbar foraminal stenosis and radiculopathy. The design will define a threshold of response utilizing both subjective and objective measures and more accurately predict excellent results following surgery.

Scientific Approach

Patients, age 18-80, who present with unilateral lower extremity radiculopathy due to degenerative foraminal stenosis will be considered for this study. Patients will be included if they present with radiculopathy and with imaging and/or clinical history or physical exam that does not demonstrate a clear neurogenic source of their pain. Examples include MRI with multi-level foraminal stenosis or discordance between MRI and clinical radiculopathy. All patients enrolled in the study will undergo a SNRB of the suspected symptomatic nerve root. Patients will undergo lumbar foraminotomy regardless of the response to the injection.

Patients will be excluded if there is a clear correlation between imaging and radiculopathy. An example would be an L5 radiculopathy in the face of an acute L4/5 herniated disc. Additional exclusion criteria include: radiculopathy associated with trauma, tumor or infection. Non-radicular lower extremity pain will also be excluded. Patients who cannot tolerate the SNRB without IV sedation will not be enrolled.

Subjects must be available for the entire study duration (12 months) and willing and able to comply with scheduled visits including completing pain diary and all patient reported outcome questionnaires.
Patients will be contacted by phone during the study follow-up (48 hours post injection).
Other exclusion criteria:
Surgery requiring multi-level decompression and/or fusion
Surgical indication for malignancy, injection or acute or emergency trauma
History of major surgery within 3 months prior to enrollment
Pregnant females
Presence of severe acute, chronic medical or psychiatric condition

Patients meeting inclusion criteria and following signing of the informed consent will undergo SNRB prior to surgery. **The surgeon will be blinded to the**

response to the injection. Patients will proceed to surgery regardless of their response to injection.

Description of Procedures

1. Pre-Injection Pain and Functional Assessment
   Prior to the injection the patient will report pain and functional status via tablet. Outcome measures recorded include VAS leg pain, ODI, PDQ and EQ-5D.
   Patients will perform a 30-meter walk test. For this test, the patient will start from a sitting position. When begun, the patient will rise and walk a pre-measured and level 30 meters. The time to conduct the test as well as a count of cadence will be performed by the research coordinator. A post walk VAS leg pain will be recorded immediately following the walk test.
2. Selective Nerve Root Block
   A single interventionalist in an ambulatory surgical center will perform all injections. Injections will be performed utilizing biplanar fluoroscopy to appropriately localize the foramen of interest and optimal needle placement. Patients will not be administered IV analgesic or anxiolytic medications. After prone positioning, the skin in the lumbar region of interested will be prepped and draped per hospital protocol. One milliliter of 1% lidocaine will be injected as a wheel into the skin in the planed incision. The injection needle will then be inserted into the anterosuperior aspect of the foramen via biplanar fluoroscopy. After confirmation of appropriate placement, 0.5 milliliters of nonionic contrast will be injected and a “radiculogram” confirmed. Epidural spread or vascular uptake of contrast will require abortion of the injection. The patient will be rescheduled for one week later for a repeat injection attempt. Inability to perform an adequate injection (i.e., lack of epidural spread) will result in exclusion of the patient from the study. To be confirmed accurate the injection should replicate the patient’s presenting radicular pain. 0.3 milliliters of 0.5% bupivacaine will then be injected into the foramen. The patients response to injection will be recorded: did the injection of contrast replicate the patients pain; did the injection of bupivacaine result in both motor and sensory changes associated with the nerve injected? Adequacy of injections (i.e., needle location and contrast spread) will be reviewed by a third party (saved fluoroscopic images).
3. Post Injection Pain and Functional Assessments
   Following recovery of the injection, the patient will report a post-injection VAS leg pain score. The patient will then perform a post injection 30-meter walk test. Time and cadence count will be recorded as well as post walk test VAS leg pain. Patients will resume normal activities and given a pain diary.
4. 48 Hour Post Injection Assessment
   At 48 hours post injection, all patients will be called. A 48-hour VAS leg pain will be assessed and pain diary reviewed. The duration of pain

change will be recorded. The change will be based on the minutes elapsed since pain improved post injection and the number of hours it took to return back to baseline.

5. Lumbar Foraminotomy
   All operations will be performed at the main campus Cleveland Clinic by a fellowship trained spine surgeon. After induction of general anesthesia and patient positioning, the lumbar skin will be prepped and draped per hospital protocol. A preoperative lateral radiograph will confirm the level of incision. The smallest incision possible will be made and subperiostial exposure utilized to expose the level of foraminotomy. The spinous process is next resected and a laminotomy performed on the index ipsilateral side. Following medial facetectomy, Kerrison Rongures will be utilized to remove overgrown bone and ligamentum flavum to decompress the neural foramen. Discectomy may be required to fully decompress the existing nerve root. The easy passage of a Woodson elevator through the foramen will be utilized to confirm adequate opening of the foramen.
6. Following surgery all patients will be seen at 6 weeks, 3, 6 and 12 months. During follow-up, patient reported outcomes will be recorded including VAS leg, ODI, PDQ and EQ-5D. Any adverse events will be recorded and noted associated or not associated with the index operation. **Any patient without improvement in symptoms 3 months post surgery will undergo MRI to assess adequacy of foraminal decompression.**
7. An excellent surgical outcome will be defined at as 15-point improvement in ODI, 26 point improvement in PDQ, improvement in VAS leg pain to 0-2, and improvement in quality of life per EQ5D.

Statistical Analysis

To improve the diagnostic value of SNRB, a threshold between positive and negative responses will be set that is best able to predict whether a patient will have a good surgical outcome. To measure the response to injection, post-injection VAS pain scores and functional assessments will be compared to pre-injection values for each patient.

First, the functional and VAS pain measures of improvement will be analyzed individually. A positive functional response to injection will be defined by setting thresholds in the timed 30-meter walk test that best differentiates patients who respond to surgery from those who do not. The accuracy of the test will be defined by its sensitivity and specificity and by its negative and positive predictive values. Separately, a threshold defining a positive response to injection will be set using VAS leg pain improvements over pre-injection values.

Then, a logistic regression analysis will be performed, including pain assessments and walk test improvements as predictors. This model will assign a value between 0 and 1 that represents how likely it is that a patient who responds to SNRB with some amount of reduction in leg pain and improvement in

functional ability has a good surgical outcome. A threshold in the model's predictive values will be set to define a positive response to the injection. This will again be done to maximize its diagnostic accuracy with respect to sensitivity and specificity and to positive and negative predictive values.

Positive and negative predictive values and their 95% confidence intervals will be reported both for the individual analyses and for the combined logistic regression analysis. Lastly, variable selection will be performed in an attempt to simplify the logistic regression model.

Due to the fact that a threshold response to SNRB has not been studied, we are not able to perform an adequate power analysis. We will use the data from this pilot study to perform a power analysis for a planned larger randomized trial. To have an adequate sample yet complete the study in a 12 month time period we plan to enroll 50 patients.

Plans for Dissemination of Results

We plan to disseminate the results of this study in multiple venues. First, we will plan to submit the results via abstract for presentation at the Lumbar Spine Research Society Annual Meeting. The results of this study will also be submitted for publication. All presentations and publications will acknowledge the Lumbar Spine Research Society.

The results of this pilot study will be utilized as pilot data for the submission of a larger multicenter prospective trial. When completed the results will also be submitted for presentation at the LSRS annual meeting and for publication. We anticipate multiple publications originating from a larger study. All presentations and publications will acknowledge the Lumbar Spine Research Society.

Future Funding and Next Steps

The preliminary results from this study will be utilized as data for a larger randomized multi-center study. This pilot study data will help formulate a proper power analysis for the design of a larger study. Moreover, the pilot data will permit insight into the threshold effect of SNRB, which can be used in the design phase of a larger study. We plan to submit an NIH RO1 grant in collaboration with other major spine academic centers. With the expenditures on therapeutic and diagnostic injections increasing each year and significant questions regarding their efficacy, we believe the NIH would be very interested in funding such a study.

Following completion of this study, we will first use the data to design a multi-center study. We believe that the data from this study will help us understand the proper SNRB to be performed and define what it truly means to have a "positive" injection. Moreover, we believe our study will define a threshold response for a

positive or negative injection. This data will then aid in the design of an appropriate much larger study. Our plan is to collaborate with our peers at large interdisciplinary spine centers in conducting a multi-center prospective study.

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