Surgery Prevention by Transforaminal Injection of Epidural Steroids for Cervical Radicular Pain (SPIES): a Randomized, Controlled Trial

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Background and Rationale

Cervical radicular pain is a common cause of disability and pain in the upper extremity and neck with an annual incidence of 83.2/100,000 (1). The initial treatment is conservative and includes relative rest, use of anti-inflammatory and analgesic medication, as well as physical therapy and home exercise. For patients who have persistent and significant symptoms, interventional pain management and surgical management are considered. Cervical epidural injections are the mainstay of the interventional, non-surgical modalities. They can be considered to provide short and long-term relief when disc herniation, foraminal stenosis or central canal stenosis pathology is identified.

Cervical epidural injections can be performed by two different approaches, transforaminal and interlaminar. Transforaminal epidural injections allow delivery of medication to the ventral epidural space, while the interlaminar approach reaches the ventral epidural space in only 28% of injections (2-4). The results of cervical epidural injections remain controversial and their efficacy in decreasing the need for surgery in patients who would otherwise be operative candidates has not been thoroughly investigated. Studies have been limited by small sample sizes, lack of control groups, and lack of randomization. Kolstad et al reported that 23% (5/21) of patients waiting for cervical disc surgery cancelled surgery when assessed at four months after having a series of two cervical epidural injections (6). Lin et al reported that 63% (44/70) of patients who were deemed to be surgical candidates were able to avoid surgery with an average of 13-month follow up (7). Lee et al reported that over 80% of 98 patients evaluated with cervical radiculopathy were able to avoid surgery with a 2-year follow-up (8). Anderberg et al reported that there was no short-term difference in symptoms of cervical radiculopathy between patients who received transforaminal injections of steroid with local anesthetic versus saline with local anesthetic. However, this study did not evaluate whether the injections were successful in the patients avoiding surgery (11).

In terms of lumbar transforaminal epidural injections, Riew et al demonstrated that steroid injections obviated the need for surgery in patients with lumbar radiculopathy. Moreover, Reiw et al showed that steroid combined with local anesthetic was more effective than local anesthetic alone in a prospective, randomized, controlled, double-blinded study (9). Riew et al later studied the efficacy of cervical transforaminal epidural injections in the same fashion, but the findings were not statistically significant ($p<0.35$) and not published (10).

We are not aware of any published prospective, randomized, controlled, double-blinded studies demonstrating the efficacy of cervical transforaminal epidural steroid injections. However, the North American Spine Society (NASS) Review and Recommendation Statement states that based on the literature and expert opinion, a minimum of one or

two cervical epidural steroid injections would be very appropriate in the treatment of a specific episode of cervical radicular pain. This literature also suggests that a maximum of four injections can be used within six months, assuming there was a positive response and improvement seen with the previous injections.

Study Design
This is a randomized, double-blinded clinical trial. The total enrollment goal is 60 patients (30 per treatment group)

Objective
The purpose of this study is to determine the effectiveness of cervical transforaminal epidural steroid injections in decreasing the need for an operation in patients with cervical radicular pain, otherwise considered to be operative candidates.

Treatment Groups:
Patients will be randomized in a 1:1 fashion to one of the following treatment arms:

1. Cervical transforaminal injection: 1.0 cc Lidocaine 1.0% with 1.0 cc normal saline
2. Cervical transforaminal injection: 1.0 cc Lidocaine 1.0% with 1.0 cc of Dexamethasone (10 mg/cc)

Primary/Secondary Outcome Variables

Primary Outcome Variables: The primary outcome variable is the avoidance of surgery. Treatment success is defined as the avoidance of surgery, while treatment failure is defined as having surgery due to failure of the injection treatment to alleviate pain and improve function over the 12 months they are being followed for purposes of this study.

Secondary Outcome Variables: Secondary outcome variables include:

- Decreased disability as measured by the validated outcome measure tool, the Neck Disability Index (NDI).
- Decreased neck pain and radicular pain as measured by a numerical pain rating, Verbal Numeric Pain Score with 0 being no pain and 10 being the worst pain imaginable
- Patient Satisfaction as measured by a numerical pain rating, Verbal Numeric Pain Score with 0 being completely unsatisfied and 100 completely satisfied

Patient Selection and Treatment Plan
Patients deemed to be surgical candidates for the treatment of cervical radicular pain at OrthoCarolina, PA will be screened for eligibility and asked to participate in the study. Potential subjects will meet with a research coordinator to discuss the details of the study. Those who choose to participate will be consented accordingly.

Inclusion Criteria:

1. Subjects who have cervical radicular pain without significant neurologic deficit (neurologic deficit is defined as manual muscle testing less than 3/5), MRI/CT findings of neural compression (neural compression is defined as disc herniation or central or foraminal spinal stenosis),
2. Failed 6 weeks of conservative treatment (conservative treatment is defined as relative rest, home exercise, physical therapy, and use of anti-inflammatory and/or analgesic medications),
3. Deemed to be good operative candidates by spine surgeons (patients with MRI/CT findings of neural compression with concordant symptoms) and had agreed to possible operative intervention

Exclusion Criteria:

1. History of
    a. acute trauma,
    b. diabetic neuropathy,
    c. active infection,
2. Active progressive neurological deficit (neurologic is deficit defined as manual muscle testing less than 3/5),
3. Medical condition that may affect the cervical spine neurological exam and/or pain assessment (e.g. peripheral neuropathy),
4. More than one cervical level requiring injection,
5. Previous cervical fusion surgery,
6. Bleeding disorders or other medical contraindications to the injection procedure,
7. Absence of substantial radicular pain (radicular pain is defined as arm pain greater than neck pain),
8. Involvement in workers' compensation claim, or any litigation related to neck injury.
9. Patients who are pregnant, or who plan to become pregnant in the next 12 months

Data Collection and Treatment Administration

Data Collection

<u>Screening Visit</u>

The primary operator or blinded investigator and/or designee will screen patients for potential participation in the study. The following data points will be collected for all patients:

- Informed Consent
- Patient demographics (medical record number, age, gender, ethnicity, body mass index (BMI),

- Patient medical history (smoking history, acute trauma, diabetes (type I or type II), active infection, active progressive neurological deficit, bilateral disease, bleeding disorders or other medical contraindications to the injection procedure, presence of radicular pain)
- NDI questionnaire (disease specific measure), Verbal Numeric Pain Score, Pain Medication Use, and Neurological Exam

Blinding

This is a double-blind study (i.e., the patient and the blinded investigator are both unaware of the specific study treatment being administered).

This protocol requires two types of investigators: **primary operators** and **blinded investigators**. The principal investigator and co-investigator(s) will determine who serves as primary operator and blinded investigator for each site. The site must clearly designate these roles prior to initiation of the study.

The **primary operator** will perform the primary study procedure. The primary operator is not blind to study treatment as he/she has to deliver the assigned therapy.

The **blinded investigator** will be blinded to study treatment and will perform all follow-up medical evaluations.

Methods used to preserve blinding are described in the relevant sections below.

Randomization

After obtaining informed consent, patients will be randomized by independent party to one of the two treatment groups. Patients will be randomized to either receive Cervical transforaminal injections with 1.0 cc of preservative-free lidocaine 1.0% and 1.0 cc of normal saline, or to receive Cervical transforaminal injections with 1.0cc of preservative-free Lidocaine and Dexamethasone (10mg/cc). A 1:1 randomization schedule will be followed. A random number generator will be used to determine the randomization schedule.

Within the operating room, staff will open the **sealed Randomization Envelope** (which has been prepared for the site in sequential order). Envelopes will be opened in the order for which patients are treated. The staff will notify the primary operator as necessary. **Do NOT call out the randomization; show the primary operator the randomization sheet within the envelope.** The randomization sheet will be filed in the patient's surgery center records and the primary operator will be instructed to dictate that the patient had a study injection and will not disclose the randomization.

Treatment Administration

Subjects will be scheduled to receive up to four cervical transforaminal injections after randomization. The injections will be scheduled at least 14 days apart and they will

receive no more than four injections within the 12 month period per the North American Spine Society (NASS) Review and Recommendation Statement.

The study procedure is performed by the primary operator. The blinded investigator must not be present.

Standardized procedure to be performed by OrthoCarolina physiatrists, using a technique similar to the following:

Patient will be sterilely prepped with a triple scrub of Betadine solution and sterilely draped. Careful attention will be paid to aseptic technique throughout the procedure. The appropriate cervical neural foramen will be identified under fluoroscopic guidance. The overlying skin and subcutaneous tissues will be anesthetized with approximately 1.0-3.0 cc of 1% Lidocaine. A spinal needle will be inserted down to the neuroforamen and into the epidural space. Approximately 1.0-3.0 cc of iodinated contrast will be infiltrated under real-time fluoroscopy and digital subtraction angiography to demonstrate satisfactory spread along the exiting spinal nerve and tracking into the epidural space without vascular uptake. This will be verified by spot films. A solution containing either a) 1.0 cc of preservative-free Lidocaine 1.0% and 1.0 cc of normal saline, or b) 1.0 cc of preservative-free Lidocaine 1.0% and 1.0 cc of solution (non-particulate) Dexamethasone (10 mg/cc) will be slowly infiltrated around the spinal nerve and into the epidural space under real-time fluoroscopy. There should be good contrast washout. The needle will be removed.

The primary operator will not have any further contact with the patient unless in the case of a medical emergency. All post-procedure assessments will be completed by the blinded follow-up physician (or designated blinded study personnel) as directed in the protocol. This includes the neurological exam and blinding assessment questionnaire.

Follow-up Phone Calls to Patient/Additional Injections
Patients will be scheduled for two (2) injections initially; these will be at least 14 days apart. One week (± 3 days) after the first injection subjects will be contacted by phone. The study coordinator will tell the subject their baseline, pre-procedure Verbal Numeric Pain Rating (a verbal assessment of pain using an 11-point scale of 0 – 10, with 0 = No Pain, and 10 = Worst Pain Imaginable) for radicular pain, and ask the subject to rate their current radicular pain intensity. Patients will also be asked to rate their overall satisfaction with their treatment and their current narcotic medication use. In the event that the subject wishes to decline the additional injection(s), the following steps will be taken:

Refusal of second injection:
If the subject's pain rating score has decreased and the subject reports satisfaction with the results of the first injection, the second injection may be cancelled after review and approval by the investigator. The patient will continue to follow-up at the remaining study intervals (i.e., 4 weeks, 12 weeks, 6 months, 12 months). If the patient requires

another injection at a later date (i.e., the pain relief from the first injection was temporary), then they may receive up to 3 additional injections within a 12 month period.

If the subject's pain rating score has increased or the subject reports dissatisfaction with the results of the first injection, the second injection may be cancelled after review and approval by the investigator and the patient will be referred back to the surgeon to proceed with the procedure.

Third and Fourth Injections (as needed)
Patients may schedule a third and fourth injection as needed. The study coordinator will call the patient one week (± 3 days) after the subsequent injection(s). The study coordinator will tell the subject their baseline, pre-procedure Verbal Numeric Pain Rating (a verbal assessment of pain using an 11-point scale of 0 – 10, with 0 = No Pain, and 10 = Worst Pain Imaginable) for radicular pain, and ask the subject to rate their current radicular pain intensity.

Refusal of fourth injection:
If the subject's pain rating score has decreased and the subject reports satisfaction with the results of the third injection, the fourth injection may not be scheduled. The patient will continue to follow-up at the remaining study intervals (i.e., 4 weeks, 12 weeks, 6 months, 12 months). If the patient requires another injection at a later date (i.e., the pain relief from the third injection was temporary), then they may receive up to 1 additional injection within a 12 month period.

If the subject's pain rating score has increased or the subject reports dissatisfaction with the results of the third injection, the patient may be referred back to the surgeon to proceed with the procedure.

Study patients can elect to abandon the injection treatment and elect to undergo surgical treatment at any point during the course of the study. It is defined as treatment failure if a study patient elects to undergo surgical treatment. Patients who elect to undergo surgery will be discontinued from the study and no further effectiveness evaluations will be performed. Patients, referring physicians, and evaluating physician assistants are blinded to the treatment group. The treating physiatrist will not be blinded to the medications but will not be performing any clinical follow-up exams.

Follow-up Office Visits
Patients will be asked to return to the clinic 4 weeks, 12 weeks, 6 months, 12 months (following their first injection date) and the following data points will be collected for both groups:

- NDI questionnaire (disease specific measure), Verbal Numeric Pain Score, Blinding Assessment (patient and investigator), Pain Medication Use, Neurological Exam, and Subject satisfaction.

In the event that the patient receives their second, third, or fourth injection within 1 week prior to one of their follow-up office visits, the post injection phone call data will be collected at that visit. The study coordinator will tell the subject their baseline, pre-procedure Verbal Numeric Pain Rating and ask the subject to rate their current radicular pain intensity. Patients will also be asked to rate their overall satisfaction with their treatment and their current narcotic medication use.
The full schedule of assessments is shown in study flow chart below.

Study Flow Chart:

Study procedure	Screening	0 (day of procedure, injection #1)	Phone Call	Injection #2 (At least 14-21 days after #1)	4 weeks post injection	12 weeks post injection	6 months post injection	12 months post injection
Informed Consent	x							
Inclusion/Exclusion	x							
Verbal Numeric Pain Score**	x		x		x	x	x	x
NDI	x				x	x	x	x
Neuro Exam	x				x	x	x	x
Injection*		x		x				
Blinding Assessment - Patient					X	X	X	X
Blinding Assessment - Investigator					X	X	X	X
Pain Medication Use	x	x	x	x	x	x	x	x
Subject satisfaction			x		x	x	x	x
Adverse Events			x	x	x	x	x	x

* Patients may receive up to four injections within the 12 month period. Injections will be scheduled at least 14 days apart.
** Patients will be called one week after injection 1, 3 (as needed), and 4 (as needed)
***If an injection occurs within 1 week prior to follow-up visits, patient will not be called. Verbal Numeric Pain Scale, Pain Medication Use, Subject Satisfaction and Adverse Events will be recorded during the follow-up visit.

Unblinding Procedures
Patients will not be unblinded to their study treatment. Unblinding of patients will only occur by the data manager and statisticians in the event of an SAE that is deemed possibly or probably related. Subjects that have been "blind-broken" must be discontinued from the study and no further effectiveness evaluations will be performed. However, the SAE will continue to be followed up until resolution.

Sample Size
Sample size calculations are based on the study by Riew et al. (2000). We estimate that 30% patients randomized to Lidocaine will avoid surgery compared to 70% of the patients randomized to Lidocaine with Dexamethasone. With a level of significance of 0.05 and power of 80%, 23 patients are needed in each group. To account for a 30% attrition rate, 30 patients are needed in each group. The total enrollment goal is 60 patients.

Risks
As with all medications, side effects may include an allergic reaction. Allergic reactions may range from minor reactions, such as itching or rash, to major, life-threatening reactions which can result in death.

Risks associated with cervical transforaminal injections include, but are not limited to:

Likely

- Spinal headache;

Less Likely

- Nerve irritation;
- Nerve injury;
- The risk of bleeding and/or infection into the spinal area;
- Reaction to medications;

Rare, but Serious

- Lung collapse;
- Seizures
- Paralysis
- Loss of vision
- Stroke
- Death.

Risks of general anesthesia or moderate sedation include, but are not limited to:

The most common side effects may include:

- Headache
- Adverse reaction to medications

Less common side effects of may include:

- Bleeding sufficient to cause anemia or require transfusion
- Hematoma (bleeding from the procedure)
- Pseudoaneurysm (injury to a blood vessel)
- Seroma (a collection of fluid under the skin)
- Blood vessel injury
- Pneumonia

Rarely, side effects may include:

- Hypotension (drop in blood pressure)
- Cardiopulmonary arrest (heart attack)
- Stroke
- Pulmonary embolism (a blood clot to your lungs)

- Death

Risks associated with contrast agents that are used in the procedure include, but are not limited to:

- Allergic reaction
- Anaphylaxis
- Death

Risks associated with the Lidocaine (anesthetic medication) that is used in the procedure include, but are not limited to:

- temporary numbness of arm
- seizures

Risks associated with the Dexamethasone (steroid medication) that may be used in the procedure include, but are not limited to:

- Hypersensitivity
- Transient jitters
- Flushing
- Elevated Blood Sugars
- Headache

Long-term and chronic use is associated with Dexamethasone use includes: avascular necrosis, osteoporosis (condition where your bones become brittle and may break easier), weight gain, or Cushing's syndrome.

Additional risks include the potential for a breach of confidentiality. The research involves the collection or study of existing data, documents, and/or records (for medical history purposes) at OrthoCarolina and Charlotte Surgery Center. Once the data is collected, the data set will be de-identified for the data analysis and manuscript. The data will be handled by OrthoCarolina/OrthoCarolina Research Institute staff and physicians and will not be shared with any external parties.

Data Management

All case report forms (CRF) will be completed and submitted for review to the Study Manager within a reasonable time frame. After approval, completed CRF's will be entered into a password protected, secure REDCap database (http://project-redcap.org/) by the data management team of OrthoCarolina Research Institute, on at least a weekly basis. REDCap is a secure web application designed exclusively to support data capture for research studies. It allows users to build and manage online surveys and databases quickly and securely with site and personnel specific usernames and passwords. REDCap provides audit trails for tracking data manipulation and user activity, as well as automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages like SPSS, SAS, and Stata. Completed CRF's and other identifiable study documents will be stored securely in a locked filing cabinet in a locked office.

Statistical analysis
Normality testing will be conducted for all continuous variables. Standard descriptive statistics will be calculated for patient demographic variables as well as the primary and secondary outcome variables. For variables measure at the ordinal level (i.e. categorical data) frequencies and percentages will be reported. Mean and standard deviation will be reported for all normally distributed data measured as intervals or ratios (i.e. continuous data). Median and interquartile range will be reported for continuous variables that are skewed. The incidence of surgery avoidance will be calculated. Bivariate analyses will be conducted to determine the associations between surgery avoidance and age, gender, pain, function, pain medicine consumption, BMI and subject satisfaction. Chi-Square tests will be used for categorical data and t-test or the nonparametric equivalent will be used for continuous data.

Adverse Event Reporting
Adverse events such as, death or any other complication will be reported to the IRB.

Subjects will be instructed to report any "Serious Adverse Event" immediately to the investigator.

"Serious Adverse Event" is defined as any event that:
- Results in death
- Is life-threatening
- Results in persistent or significant disabling/incapacity
- Requires inpatient hospitalization or prolongation of hospitalization
- Is a congenital abnormality/birth defect
- Requires medical or surgical intervention to prevent permanent impairment or damage

Serious adverse events will be reported to Presbyterian Healthcare Institutional Review Board within 24 hours of the event. This report may be done by phone initially and will follow with an adverse event report form.

Data Safety Monitoring
A Data Safety Monitoring Board will review data for integrity.

Robert Anderson, M.D., Chairman, Research Committee will serve as the safety monitor. A data safety monitoring board (DSMB) will review data on a bi-monthly basis or as needed. The DSMB are members of the OrthoCarolina Research Institute (OCRI) Research Advisory Committee.

<u>Data Safety Monitoring Plan</u>
Serious adverse events (SAEs) that are “related,” “probably related” or have an “unknown” relatedness to the study procedure, will be reported to the data safety monitoring board via email as they occur. The data safety monitoring board meets every

other month. At each meeting the study will be reviewed for adverse events, serious adverse events, and overall feasibility issues.

Ethical and Regulatory Considerations

- Informed Consent
  Informed consent will be obtained for each patient. One copy of the informed consent will be given to each patient, a copy will be placed in the medical records, and the original signed copy will be retained in the investigator's study records. The protocol and the patient informed consent will have the approval of a properly constituted IRB responsible for approving clinical studies. Any changes to the protocol will be approved by the IRB and any changes to the informed consent must be approved by the IRB.
- Applicable regulations
  This is an Investigator Initiated Research Study and will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

Records Retention
All patient records including written informed consent forms, the protocol, and IRB correspondence will be kept for a minimum of three years from the date of termination of this study.

Data Collection forms
See Attached forms

Definition of Subject Completion, Withdrawal, and Premature Discontinuation
Subject completion
A subject will be considered to be completed if the patient completes all study procedures and follow-up.

Withdrawal and Premature Discontinuation
Patients may be withdrawn or prematurely discontinued from the study of their own volition or at the discretion of the investigator. Any patient may decide to withdraw from the study at any time without being penalized. The investigator and/or anesthesiologist will discontinue the patient from the study, if, for any reason, he/she feels that the continued participation would not be in the best interest of the patient.

Study Completion and Termination
The study is completed when the desired sample size of patients have completed the study or if the investigator feels that the study should no longer continue. The institutional review board will be notified of study completion and/or termination.

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