Title: A Prospective Randomized Comparative Trial of Targeted Injection via a Transforaminal Approach with Dexamethasone versus an Epidural Catheter via an Interlaminar Approach with Particulate Steroid for the Treatment of Cervical Radicular Pain

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Objectives:

Through a research questionnaire and pre-procedure baseline testing of strength, sensory, NRS pain score and post procedure testing of strength, sensory, and NRS pain score we will obtain data regarding cervical epidural steroid injections via a transforaminal approach using corticosteroid to determine if the proposed hypothesis listed below is supported and if the null hypothesis will be rejected.

Hypothesis: Targeted cervical epidural steroid injections via a transforaminal approach using corticosteroid superior to targeted injections using an epidural catheter via an interlaminar approach with particulate steroid for improving pain and function in patients with cervical radicular pain.

Null Hypothesis: Targeted cervical epidural steroid injections via a transforaminal approach with non-particulate corticosteroid will provide no difference in pain relief or functional improvement as compared to targeted injections using an epidural catheter via an interlaminar approach with particulate steroid in patients with cervical radicular pain.

Introduction

Cervical radicular pain is a common, disabling problem that occurs in 83:100,000 individuals per year.[1] Symptoms are most often caused by intervertebral disc herniation (21.9%) or central or foraminal stenosis from spondylosis (68.4%).[2,3] Patients complain of pain in the head, neck, scapula, or arm.[4,5] The diagnosis of radicular pain is made clinically by history and physical examination, supported imaging studies, and electrodiagnostic tests.

In the absence of a progressive neurologic deficit, initial treatment of cervical radicular pain includes oral anti-inflammatory medications, activity modification, postural retraining, ergonomic adjustments, and physical therapy.[6,7] If this conservative approach fails to relieve pain, an image guided epidural steroid injection (ESI)[8-10] is the second-line treatment. Corticosteroids act primarily through the inhibition of the phospholipase A2-initiated arachadonic acid cascade,[11] thereby reducing local inflammation and intraneural edema and enhancing blood flow around the affected nerve root. Steroids also suppress transmission of nociceptive C-fibers via direct membrane stabilizing effects.[12]

Though well-conducted prospective, randomized controlled trials of CESI are few in number, a systematic review of the literature demonstrates that CESI is clinically effective in treating radicular pain.[13] When cervical epidural steroid injections were compared to intramuscular steroid injections in a clinical trial, 68% of patients treated with interlaminar cervical epidural

steroid injections had significant pain relief at one year follow-up, compared to only 11.8% of the patients receiving intramuscular injections.[14] In another study, cervical epidural steroid injections were successful in reducing pain in 80% of patients with a mean follow up period of 43 months.[15] In another clinical trial, however, only 20-26% of patients with disc herniation who failed non-interventional care experienced good to excellent results after cervical ESI.[16] Prospective, randomized, controlled studies have shown that ESI reduces the rate of spinal surgery in the lumbar spine,[17,18] and there is evidence of a similar effect related to cervical ESI.[16]

Two distinct techniques used to administer epidural steroids specifically to the nerve root affected in a radicular pain syndrome, which include transforaminal access at the level of pathology and interlaminar interlaminar access at the C7-T1 level with subsequent advancement of an epidural catheter to the level of pathology. Use of an epidural catheter is necessary in order to achieve a targeted injection via an interlaminar approach in order to prevent dural puncture or direct spinal cord trauma. Anatomic studies confirm the distance between the ligamentum flavum and dura is on average, 4 mm at the C7-T1 or C6-C7 levels, but 1mm or smaller at C5-C6 and more rostral levels.[19] Therefore, there is likely greater risk of dural puncture and spinal cord injury when "targeting" steroid delivery using only the interlaminar technique directly at the level where pathology is located (C4-C5, or C5-C6, for example).[20-23] Thus, the interlaminar placement of a needle rostral to the C6-C7 level has been strongly discouraged.[21]

Both the transforaminal injection approach and the targeted catheter approach demonstrate effectiveness. Studies have demonstrated the effectiveness of transforaminal epidural steroid injection for the treatment of cervical radicular pain.[24,25] Our own recent work demonstrates the clinical effectiveness of the catheter-based targeted approach.[26] However, these two approaches have never been directly compared. Thus, we aim to compare the differences in pain reduction, medication utilization, functional outcomes, patient satisfaction, and surgical rate reduction between these two approaches to the treatment of cervical radicular pain.

Cervical radicular pain is a common syndrome, often treated with epidural steroid injection (ESI). An approach that targets the therapeutic agent, corticosteroid, at the site of spinal pathology can be performed via a transforaminal approach or via a interlaminar approach at C7-T1 with subsequent epidural catheter advancement to the symptomatic level. There are no universal guidelines that recommend the use of one technique over the other. We will directly compare the clinical effectiveness of these two approaches as measured by pain reduction, medication utilization, functional outcomes, patient satisfaction, and surgical rate reduction. The results of this study will potentially influence clinical practice recommendations regarding the treatment of cervical radicular pain. If one technique proves superior, instating this technique will have implications potentially for reducing opioid use, surgery and other healthcare utilization, and general healthcare cost related to the treatment of cervical radicular pain.

Subjects

A total of 100 subjects, aged 18-80 on the day of enrollment, will be recruited for participation in this study. Patients will be randomized to one of two groups based on a random computer-generated schedule.

Those assigned to Group #1 will undergo a transforaminal cervical ESI and those in Group #2 will receive a catheter-targeted ESI via interlaminar access at the C7-T1 level.

De-identification

All subjects will be assigned a unique alphanumeric identifier. No personally identifiable information will be used in the final database. All data will be stored on a highly secure, password protected computer.

Participant Recruitment

Our intended subject demographic includes an active population between the ages of 18 and 80 years on the day of enrollment. We intend to recruit participants primarily through word-of-mouth and from a database or participant pool for which participants have given prior permission to be contacted for research studies. Additionally, recruiting will take place through the distribution of flyers to the Health Sciences Education Building, University of Utah Student Life Center, the University of Utah Orthopaedic Center, and the University of Utah hospital. Upon first contact with the potential participant, the study coordinator or research associate will provide a basic description of the study and review inclusion and exclusion criteria, general health status, and past and current athletic participation. Interested volunteers who qualify will be asked to report to the University of Utah Orthopaedic Center. Prior to screening procedures and after being informed of any potential risks involved in the study, volunteers will be asked to provide written, informed consent for study participation.

Inclusion Criteria:

1) Age 18-80.
2) Clinical diagnosis of unilateral C4-C8 radicular pain.
3) Magnetic resonance imaging pathology consistent with clinical symptoms/signs.
4) Numerical Rating Scale (NRS) pain score of 4 or higher.
5) Pain duration of more than 6 weeks despite trial of conservative therapy (medications, physical therapy, or chiropractic care).

Exclusion criteria:

1) Refusal to participate, provide consent, or provide follow-up information for the 6-month duration of the study.
2) Contraindications to Cervical ESI (active infection, bleeding disorders, current anticoagulant or antiplatelet medication use, allergy to medications used for CIESI, and pregnancy).
3) Cervical spinal cord lesions; cerebrovascular, demyelinating, or other neuro-muscular muscular disease.
4) Current glucocorticoid use or ESI within past 6 months.
5) Prior cervical spine surgery.
6) Patient request for or requirement of conscious sedation for the injection procedure.

Study design:
Prospective, randomized, comparative trial

Patients will be randomized to group #1 or #2 based on a random computer-generated schedule.

Group #1: Transforaminal cervical ESI with dexamethasone sodium phosphate 1.5 mL (10mg/mL) and 1 ml 1% lidocaine (total volume 2.5 mL).

Group #2: Catheter-targeted ESI via interlaminar access at the C7-T1 level with triamcinolone acetonide 2 mL (40mg/mL) and 1 ml 1% lidocaine (total volume 3 mL).

Dexamethasone will be used in the transforaminal group, while triamcinolone will be used in the catheter-based group as this represents the standard of care for preforming these injections, consistent with current safety recommendations.[21]

Adults who are eligible and scheduled to have an epidural steroid injection for cervical radicular pain at the University of Utah Orthopaedic Center will be approached by authorized research personnel. All eligible patients will be offered to participate in the study and all patients will sign a written informed consent form before proceeding and will also be consented for the procedure. Participating in the study is voluntary. The patients may choose not to enroll in the research. Patients will be presented with the same options of treatment whether they enroll or decide not to.

Power Analysis
Size of study groups: 40; 80 total participants.
The necessary sample size was determined based on a review of past literature and power analysis. While no head-to-head studies of targeted approaches to ESI have been performed in the cervical spine, such studies have been conducted in the lumbar spine. Studies that used sample sizes of 20-30 participants per treatment group showed statistically significant differences ($P < 0.05$).[27-29] We will thus plan to recruit 100 participants (50 per group) in anticipation of a 20% attrition rate by 6-month follow-up, which would still result in approximately 40 participants per group, to allow for improved power to detect a difference between groups compared to the prior cited similar literature.[27-29]

Procedures
During the injection procedure, the participant will be positioned on a fluoroscopy table. Blood pressure and pulse oximetry monitors will be placed. A pre-procedure time-out will be performed, as is protocol in the University practice. Vital signs will be recorded immediately prior to and every 5 minutes during the injection procedure as is the current practice standard. Using fluoroscopic guidance, cervical ESI using one of the two approaches based on group randomization will be performed:

Transforaminal epidural steroid injection
After injection of 1 to 2 mL of 1% lidocaine to the skin and subcutaneous tissues, a 25-gauge spinal needle will be placed at the level and side of radicular pathology, based on clinical

correlation of symptoms/signs and magnetic resonance imaging findings. Advancement to the appropriate target position in the neuroforamen will be performed under fluoroscopic guidance according to practice guidelines.[30] Once a satisfactory target position is achieved and confirmed in both anterior-posterior and oblique views, 0.5 to 1 mL of contrast (Omnipaque-240; GE Healthcare, Princeton, New Jersey) will be injected under live fluoroscopic observation with or without digital subtraction angiography depending on suggestion of vascular uptake, as is standard practice and recommended by practice guidelines.[30] Upon confirmation of a satisfactory epidural contrast pattern without vascular uptake, the injectate will be delivered: dexamethasone sodium phosphate 1mL (10mg/mL) and 0.5 ml of 1% preservative-free lidocaine (total volume 1.5 mL). After the injection procedure, participants will be observed and then discharged from the clinic with written discharge instructions (current standard practice).

Catheter-targeted ESI via interlaminar access at the C7-T1 level
After injection of 1 to 2 mL of 1% lidocaine to the skin and subcutaneous tissues, an 18-gauge 3.5-inch RX Epidural Needle (Epimed International Inc., Dallas, TX) will be placed at the C7-T1 level per practice guidelines and current safety recommendations,[21,30] and a loss of resistance (saline) technique will be used to gain access to the epidural space; needle position will be confirmed in anteroposterior and lateral views. A radiopaque styleted 21-gauge epidural catheter (C-KATH; Epimed International Inc., Dallas, TX) will be introduced through the Tuohy needle and advanced under live image guidance to the level and side of radicular pathology, based on clinical correlation of symptoms/signs and magnetic resonance imaging findings. Once a satisfactory target position is achieved with the catheter, 0.5 to 1 mL of contrast (Omnipaque-240; GE Healthcare, Princeton, New Jersey) will be injected. Upon confirmation of a satisfactory epidural contrast pattern, the injectate will be delivered: triamcinolone acetonide 1 mL (40mg/mL) and 0.5 ml 1% lidocaine (total volume 1.5 mL). After the injection procedure, participants will be observed for 20 to 30 minutes and then discharged from the clinic with written discharge instructions (current standard practice).

Repeat injections
If a repeat injection is required, the patient will remain in the study. We will perform the same injection to which the patient was randomized for the first injection. We will document how many injections are required for patients to report at least 75% improvement in neck and arm pain. No more than 2 repeat injections will be performed during the study. This protocol was used in a previous study.[26]

Data Collection:

An electronic data collection sheet (via iPad) will be used to record all pre-procedure data (see data collection sheet):

1) Age (years).
2) Sex.
3) Height (cm).
4) Weight (Kg).
5) Duration of pain (weeks).

6) Location of cervical radicular pain based on clinical diagnosis: C2, C3, C4, C5, C6.
7) Radiologic diagnosis based on MRI of the Cervical Spine.

Before an initial injection, the following measures will be obtained:
7) NRS for pain; separate scores for neck pain and for arm pain
8) Neck Disability Index (NDI-5)
9) Medication Quantification Scale (MQS III) score
10) Daily opioid use in morphine equivalents

Immediately after injection the following will be obtained:
11) Fluoroscopy time
12) Post-injection NRS pain score; separate scores for neck pain and for arm pain
13) Adverse events, if they occurred

At intervals of 2 weeks, 1 month, 3 months, 6 months, and 1 year after injection, outcome measurements will be repeated. The Patient Global Impression of Change (PGIC) and a patient satisfaction score (five-point Likert scale: 1, very dissatisfied; 2, dissatisfied; 3, neither satisfied nor dissatisfied; 4, satisfied; and 5, very satisfied) will also be recorded. A single researcher blinded to group assignment collected all follow-up assessments in person, by e-mail, by telephone, or by mailed questionnaire.

Data Storage:
Hard copy data will be collected and stored in a password-protected computer located in the Division of PM&R. Participants will each be assigned an ID number that will be used as the sole identifier on any documents. Participant data will be compiled onto a single password protected file, where they will only be identified by their ID number. An enrollment log will be the only file where subject names are correlated with ID numbers. This will be kept in a separate, secure, password-protected file in the Division of PM&R.

Data Analysis Plan
The primary outcome will be the proportion of participants with 50% or greater reduction in neck and arm pain on the NRS pain score at the 1-month follow-up assessment. Secondary outcomes included reduction in median NRS pain score (both neck pain and arm pain), NDI-5, MQS III, opioid consumption in daily morphine equivalents, PGIC score, and satisfaction score. Secondary outcomes will also be defined based on categorical "responder analysis" definitions of important clinical change given the National Institutes of Health recommendation for responder analysis in the assessment of therapeutic spine pain interventions.[31] The responder analysis will include the proportion of patients with 30% or greater improvement on the NDI-5,[32,33] a PGIC score less than 3 (indicating "improved" or "very much improved"), a 6.8 or greater point reduction on the MQS III score (equivalent to approximately 10 daily morphine equivalents),[34] and the proportion of participants who undergo surgical spine surgery.

<u>Statistical analysis</u>

Means and standard deviations of subject demographic data, as well as pain, functional, and treatment satisfaction scores will be calculated. Intergroup differences will be assessed by t test for numerical data and Chi Square or Fisher Exact test for categorical data. Regression modeling will be implemented using ANOVA to assess for patient traits and characteristics that increase the likelihood of efficacy using one technique as opposed to the other.

Risks/Benefits:

Risks of study participation are the same as those for any standard fluoroscopically guided cervical ESI frequently performed in the PM&R Spine Clinic. These include: local infection, epidural hematoma or abscess, dural puncture and potential post-dural puncture headache, paresthesia during needle placement, pain at the injection side, failure of technique, allergy to latex or medications being used. Utilizing fluoroscopy, the risk of nerve damage, spinal cord injury or intravascular injection is less than 1:500,000. The length of stay and length of recovery is no longer than that of a standard ESI performed in the PM&R Spine Clinic at present.

There are no direct benefits to the individual by participating in this study. The patients will be presented with the same options of treatment whether they enroll in the study or decide not to. The information extracted from this study may provide the investigators a better understanding of patient's pain response following a cervical epidural steroid injection.

Study Termination Criteria

- Adverse events considered/identified by the medical staff during the procedure process
- The subject requests to be withdrawn from the study during the procedure.

Safety Monitoring Plan

Safety will be monitored by all members of the study team:

Zachary McCormick, MD
Richard Kendall, MD

The Principal Investigator is an MD at the University of Utah Orthopaedic Center. Members of the data and safety monitoring committee will be in close contact with all the subjects throughout the study, both in-person and via telephone. The members of the data and safety monitoring committee will review potential side effects and adverse reactions with each subject at the time of delivery of the study drug and at the time of each sample collection. All the committee members are located at the University of Utah Orthopaedic Center; all members have research experience.

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