Comparison of cervical transforaminal epidural corticosteroid injections with lateralized interlaminar epidural corticosteroid injections for treatment of cervicogenic upper extremity radiculopathy

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Purpose of the Study

Our central hypothesis is that the innovative CT fluoroscopy-guided lateralized interlaminar epidural corticosteroid injection technique will exhibit superior or equivalent efficacy to the traditional transforaminal method for treatment of cervicogenic upper extremity radiculopathy.

SPECIFIC AIM 1: Compare the efficacy of CT fluoroscopy-guided LILESI to that of CT fluoroscopy-guided TFESI in the treatment of patients with cervicogenic upper extremity radiculopathy.
HYPOTHESIS 1: Patient outcomes will be equivalent between the two injection techniques.

1.1 Compare the difference in the primary outcome measure between the two patient groups: numerical pain rating scale (averaged over the past 24 hours) at two months.

1.2 Compare the difference in secondary outcome measures between the two patient groups: numerical pain rating scale (averaged over the past 24 hours) at 2 weeks and 4 months; neck disability index, EQ-5D, and work ability index at 2 weeks, 2 months, and 4 months.

SPECIFIC AIM 2: Compare complication rates between the two injection techniques.
HYPOTHESIS 2: No difference will be seen in complication rates between the two injection techniques.

2.1 Determine the frequency of minor and major adverse events for each group immediately post-procedure and at 2 days after the procedure.

SPECIFIC AIM 3: Determine the technical success rate, defined as the spread of the contrast epidurogram into the neuroforamen, for each of the two injection techniques.
HYPOTHESIS 3.1: The contrast epidurogram will extend into the neuroforamen more frequently with the lateralized interlaminar approach than with the transforaminal approach.

3.1 Determine the frequency of contrast spread into the neuroforamen for each group.
HYPOTHESIS 3.2: Inadvertant intravascular injection will occur more frequently with the transforaminal approach.

3.2 Determine the frequency of inadvertent intravascular contrast injections for each group.

Background & Significance

Cervicogenic radiculopathy is a common problem with an age-adjusted incidence rate of 83 per 100,000 annually (1). A variety of non-surgical treatment options are available including physical therapy, oral pharmacotherapy, and corticosteroid injections. The utilization of cervical epidural corticosteroid injections (CESI) for treatment has progressively increased over the past decade, now numbering in the millions annually in the United States (2). There are two methods for performing CESI: the interlaminar approach and the transforaminal approach. An interlaminar epidural steroid injection (ILESI) involves a posterior needle approach to place the needle tip within the dorsal epidural fat of the spinal canal along the midline. The transforaminal epidural steroid injection (TFESI) involves a lateral needle approach to place the needle tip within the neuroforamen adjacent to the inflamed nerve root (Figure 1A). Many postulate that cervical TFESI is superior in efficacy to ILESI due to more accurate delivery of medication to the inflamed nerve root. However, prospective clinical trials have not been performed to confirm this supposition.

CT fluoroscopic guidance allows for exceptional precision in needle placement because acquired axial images provide excellent information about needle depth and allow for direct visualization of soft tissue structures including the ligamentum flavum, target nerve root, and the vertebral artery. These soft tissue structures are unable to be visualized with conventional fluoroscopy. ILESI is rarely performed above the C6/7 interspace using conventional fluoroscopy due to the inability to directly visualize the ligamentum flavum, known discontinuity of the ligamentum flavum in the cervical spine (precluding reliance on "loss of resistance" technique), as well as the diminutive size of the target dorsal epidural fat (typically 1 -2 mm) (3, 4). These limitations are not present with CT fluoroscopic guidance. Our group has successfully performed thousands of CT fluoroscopy-guided ILESI at every level throughout the cervical spine (5).

Performing an ILESI in which the needle is placed in the far lateral dorsal epidural space adjacent to the facet joint and target neuroforamen, rather than the midline, may result in excellent delivery of medication to the inflamed nerve root. This lateralized interlaminar epidural steroid injection (LILESI) technique has recently been attempted in the lumbar spine where it has been shown to demonstrate equivalent efficacy to TFESI for treatment of lumbar radiculopathy (6, 7). However, this technique has not been studied in the cervical spine and the utility of CT fluoroscopy has not been assessed. Given the excellent precision with needle placement under CT fluoroscopy guidance, it is well suited for performing LILESI in the cervical spine.

The proposed study is innovative because it will be the first to employ CT fluoroscopy-guided LILESI in the treatment of cervicogenic upper extremity radiculopathy. It is also the first study to directly compare treatment efficacy between this new injection type with that of the traditional transforaminal epidural approach. This is significant because demonstration of superior efficacy for LILESI could lead to a paradigm shift in the treatment algorithm for this patient cohort away from TFESI. Additionally, this study could lead to a significant change in practice patterns with a shift toward CT guidance for treatment of cervicogenic radiculopathy, since the LILESI approach cannot be performed under conventional fluoroscopy.

Design & Procedures

Cervical Epidural Corticosteroid Injections

We will employ a single-center, parallel, randomized, prospective design. Enrolled patients will be assigned to one of two treatment arms using a block randomization scheme: transforaminal cervical epidural corticosteroid injection or lateralized interlaminar cervical epidural corticosteroid injection. Baseline data will be collected including duration, location, and character of pain; numerical pain scale (NRS); neck disability index (NDI); EQ-5D; and work ability index (WAI) (see Outcome Measures below). All procedures will be performed under CT fluoroscopy on the same scanner. The cervical level of injection for patients in both treatment arms will be at the discretion of the treating physician and will be based on symptoms (e.g., dermatomal distribution of pain) and imaging findings. All injections will be performed by a board certified radiologist with a certificate of added qualification in neuroradiology and at least five years of experience in CT fluoroscopy-guided spine injections. Patients and outcome assessors (clinical research coordinator) will remained blinded to the treatment assignment throughout

the study. In order to maintain blinding of patients and appropriate study personnel throughout the trial, billing / charges will be held until the patient reaches the final endpoint of the study or withdraws from the study. The research coordinator will be the study personnel who records the billing at this point, however, all outcome assessments will have been completed already ensuring that they remain unbiased. The treating physicians are unable to be blinded, as they will be aware of the type of patching material used. The effectiveness of patient blinding will be assessed using the Bang Blinding Index prior to discharge on the day of the procedure (8). Patients will become unblinded to their treatment assignment at the end of their participation in the study (either at the conclusion of the study after the final outcome measure time point (i.e. 4 months) or if they elect to withdraw from the study at any time).

Transforaminal Cervical Epidural Corticosteroid Injections (TFESI)

Patients randomized to undergo TFESI will be placed supine on the CT gantry table. A planning CT scan (120 kVp, automatic tube current modulation: 100 – 400 mA, 2.5 mm section thickness, rotation time 0.5 seconds) will be obtained with z-axis limited to the area of interest. Acquired images will be used to plan a lateral approach needle trajectory, as previously described (9). The skin surface will then be marked, sterilized, draped, and anesthetized. A 22-gauge 1.5 or 3.5 inch Quincke tip spinal needle will be advanced under intermittent CT fluoroscopic guidance into the posterolateral aspect of the neuroforamen (Figure 1A). On reaching the target, gentle aspiration will confirm absence of blood return. Approximately 0.2 mL of contrast material (iopamidol; Isovue-M 200, Bracco Diagnostics, Princeton, NJ) diluted 1:3 with preservative free normal saline will then be injected to assess needle tip position and potential future medication spread. Intravascular injection is excluded using a "double-tap" technique (i.e., 2 sets of CT fluoroscopic images: an initial image immediately after injection and a second image acquired 2-3 seconds later to assess for contrast material washout), as previously described (10). After visual confirmation of safe needle tip positioning, a test injection of approximately 0.5 mL of 1% lidocaine will exclude symptoms suggestive of intra-arterial injection (alteration in sensation, motor weakness, metallic taste, seizure). Finally, 0.8 mL of dexamethasone (10 mg/mL) will slowly be injected over a period of approximately 30 seconds. On completion of the procedure, the patient will be observed for 30 minutes in the Radiology Observation unit.

Lateralized Interlaminar Epidural Corticosteroid Injections (LILESI)

Patients randomized to undergo LILESI will be placed prone on the CT gantry table. A planning CT will be obtained through the area of interest. Acquired images will allow for planning a posterior approach lateralized interlaminar needle trajectory to the dorsal epidural space. The skin surface will then be marked, sterilized, draped, and anesthetized. A 22-gauge 3.5 inch Quincke tip spinal needle will be advanced under intermittent CT fluoroscopic guidance into the lateral dorsal epidural space (Figure 2). On reaching the target, heme-negative aspiration will be confirmed. Next, approximately 0.2 mL of contrast material (iopamidol; Isovue-M 200, Bracco Diagnostics, Princeton, NJ) diluted 1:3 with preservative free normal saline will be injected to assess needle tip position and potential future medication spread. Intravascular injection will be excluded using a "double-tap" technique. After visual confirmation of correct needle tip position, 0.8 mL of dexamethasone (10 mg/mL) will slowly be injected over a period of approximately 30 seconds. On completion of the procedure, the patient will be observed for 30 minutes in the Radiology Observation unit.

Patient Outcome Measures

Prior to the procedure, baseline outcome measures of NRS, NDI, EQ-5D and WAI will be determined (see Outcome Measures below for description). Immediately post-procedure, NRS will be reacquired. NRS, NDI, EQ-5D and WAI will then also be acquired via mail, electronic communication, or telephone call at 2 weeks, 2 months, and 4 months post-procedure. The primary endpoint will be NRS (averaged over the past 24 hours) obtained at 2 months after the procedure. Secondary endpoints will include NRS at 2 weeks and 4 months after the procedure as well as NDI, EQ-5D and WAI at 2 weeks, 2 months, and 4 months after the procedure.

Adverse Events

Patients will be screened for adverse events immediately after the procedure as well as via phone call at 2 days post-procedure. While all adverse events will be recorded, the following will be considered major adverse events: stroke, paralysis, or other permanent neurologic deficit; allergic reaction; hospitalization or ER visit. Minor adverse events will include, but not be limited to: nausea / vomiting, dizziness, headache, symptomatic hypertension, vasovagal reaction, fever / chills, facial flushing, insomnia, and pain exacerbation.

Epidurogram

The primary investigator will retrospectively evaluate epidurographic contrast material spread through review of the procedural images at the completion of the study. The leading edge of resultant contrast during both the TFESI and LILESI groups will be categorized as either within the spinal canal, intraforaminal, or extraforaminal, as previously described in publications by our group (see Figure 1B) (11). The presence of inadvertent intravascular injection will also be noted, as previously described by our group (10).

Crossover, Withdrawal, or Missing Data

We will employ an intention-to-treat (ITT) analysis for this trial [49]. All persistently symptomatic patients, regardless of study arm (i.e. both LIESI and TFESI), will be allowed to crossover at the 2-month time point. Patients that crossover between study arms, withdraw from the study, or for whom there is missing data will all be handled in the same manner: we will conservatively assume that no further benefit will be gained from the initial treatment. As such, the most recent available outcomes data will be extrapolated to all later time points for which no data are available. Patients will be allowed to withdraw from the study and terminate their participation at any time.

Interim Data Analysis

An interim analysis will be performed of the first 58 patients by the biostatistician. All study participants, outcome assessors, and other personnel will remain blinded. Safety and efficacy will be evaluated using an O'Brien–Fleming stopping rule of $p < 0.001$ in order to evaluate for early evidence of treatment efficacy [48].

Outcome Measures

Numerical Rating Scale (NRS)

The pain numerical rating scale (NRS) is a well-validated tool for quantitatively assessing patients' pain (12). The NRS asks patients to rate their current pain intensity on an 11-point scale ranging from 0 ("no pain") to 10 ("worst possible pain"). It has been found to be a valid measure of pain intensity with minimum clinically important difference noted to be a change of 2 points (13, 14). We will use NRS averaged over the past 24 hours for all time points in this trial. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement indicates that an NRS reduction of 30% (or 2 points) is associated with a meaningful or moderately important improvement in pain. Further, IMMPACT also indicates that an NRS reduction of 50% (or 4 points) is associated with a substantial improvement in pain. We will follow their consensus recommendations and explicitly report these two categories of pain relief (15).

Neck Disability Index (NDI)

The NDI a well-validated measurement tool that contains 10 items: seven related to activities of daily living, two related to pain, and one related to concentration (16). Each item is scored from 0 to 5 and the total score is expressed as a percentage, with higher scores corresponding to greater disability. The NDI has documented acceptable levels of responsiveness and construct validity when used in patients with cervical radiculopathy (17).

EQ-5D

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (18). It is a well-validated tool for health status measurement (19), and for health quality-of-life in cervicogenic radicular pain (20).

Work Ability Index

The Work Ability Index (WAI) is a validated, reliable measure of a worker's ability to do his or her job that has been shown to predict work disability, retirement and mortality (21). The questionnaire demonstrates excellent test - retest reliability (22).

All data will be collected in a password-protected file and will be stored in an electronically secure environment, as specified in the research data security plan (RDSP).

Selection of Subjects

Adult patients with unilateral cervicogenic upper extremity radiculopathy (with or without accompanying neck pain) and a baseline numerical pain scale (NRS) score > 4 will be recruited from the Duke Radiology and Orthopaedic spine intervention clinics. Exclusion criteria include: (a) recent (i.e., < 2 months) cervical spine surgery, (b) recent (i.e., < 1 month) cervical epidural or upper extremity corticosteroid injection, (c) contraindication or inability to the undergo procedure, (d) inability to provide informed consent, (e) expected inability to complete follow-up assessment, or (f) a contraindication to receiving contrast material (precluding an epidurogram). We aim to recruit 116 patients over 1 year. This number is based on the historical number of patients treated with unilateral

cervical radiculopathy, our sample size determination (see Statistics), and previously published studies in the lumbar spine (7).

We estimate that approximately 1000 patients will be screened over one year in order to reach our target recruitment of 116 patients.

Subject Recruitment and Compensation

At the time of the patient's phone call to our office for the purpose of scheduling their procedure, patients referred to our team for treatment of cervicogenic upper extremity radiculopathy will be asked by our staff if they would be potentially interested in discussing a clinical trial. Those that are not interested will not be further contacted about the study. Those that are willing to discuss further will then be referred to our clinical research coordinator (CRC). The CRC will contact the patient (at least one day) prior to their arrival to our clinic for the injection (see attached phone script). At the time of this phone call, potential subjects will be given an overview of the study and then asked if they are interested in participating. If they are interested in participating, the MD performing the injection (either Dr. Amrhein or Dr. Kranz) will be notified on the day of the patient's procedure. At the time of the patient's visit, the MD will discuss with them their pain pattern, imaging findings, and diagnosis, and will explain how CT guided cervical epidural corticosteroid injections are performed as well as a discussion of the risks and benefits of these procedures. This will all be done prior to any discussion of the clinical trial. At this point, if a potential subject meets the inclusion and exclusion criteria, the CRC will be notified and written informed consent will be obtained from the patient by the CRC on the date of the patient's procedure using the standard IRB-approved consent processes.

Study Interventions

The main intervention in this study is randomization into either of the two treatments arms (described in detail above). This should have negligible effect upon the patients as there is no known difference in risk between the two procedures and the difference in the efficacy between the two procedures is unknown (and the purpose of this study).

Risk/Benefit Assessment

Because both injection types investigated in this study (LILESI and TFESI) are currently used in our institution as part of standard-of-care for treatment of cervical radiculopathy, there is no excess medical risk to subjects as a result of the study randomization.

Study participants will be randomized to receive a cervical epidural steroid injection of 0.8 mL of dexamethasone (10 mg/mL) through either a lateralized interlaminar or a transforaminal route. Cervical epidural injections via both routes have had reports of minor (increased pain, passing out, headaches, insomnia, hiccups, minor allergic reactions) and major (bleeding, major allergic reaction, paralysis,

stroke, death) adverse events. These would be disclosed to the patient during the process of informed consent for the procedure. Even though patients may provide consent to a cervical epidural steroid injection, we acknowledge that this protocol involves removing participant and provider choice and randomizing participants to one route or another. However, the peer-reviewed literature is clear that there is no data to support the notion that one route exposes a recipient to increased risk (23) and both routes continue to endorsed in the most recent edition of Spine Intervention Society Guidelines.(24) This protocol will mitigate procedural risks through the exclusion of any prospective participants where such injections are contraindicated; and through the use of highly-experienced and fellowship trained operators, using image-guidance, contrast-confirmation, and non-particulate dexamethasone consistent with the Multi-Disciplinary Pain Working Group's recommendations (25) and Spine Intervention Society Guidelines.(24) Any adverse events will be reported according to protocol.

We do not anticipate any incremental physical or medical risks to study participants, as no additional medical procedures or interventions will be performed as part of this study. The act of completing outcome questionnaires may create small risks to some participants. These risks are minimal and involve disclosing potentially uncomfortable or mildly distressing information about anxiety and quality of life. This risk is not expected to exceed what the participants would routinely encounter in their day-to-day lives or at a medical appointment. An additional risk is the mild inconvenience of completing the forms. Estimated times to complete these outcome measures will be disclosed to prospective study participants. Vulnerable populations, such as children, prisoners, and cognitively impaired adults will not be included in this protocol. Pregnancy is an exclusion to the standard-care use of CT fluoroscopy (imaging guidance). Therefore, women of childbearing potential will be questioned about the possibility of being pregnant. This will include obtaining a menstrual history as well as information about contraceptive use and sexual activity. If there is uncertainty about the possibility of pregnancy, then a serum pregnancy test will be administered to determine if the patient is a candidate for enrollment in the trial. There is not expected to be any direct benefit to the patient from participation in this randomized trial. Patients who choose to not participate will continue to receive all standard care appropriate to their presenting complaint. However, the importance of the knowledge gained from this study will improve our understanding of the efficacy of cervical epidural steroid injections in patients with cervical radicular pain.

Another potential risk associated with any research that involves data storage is the potential risk of loss of confidentiality. This will be minimized by adherence to the research data security plan (RDSP) submitted as part of all IRB-approved studies conducted at Duke University Medical Center.

Data Analysis & Statistical Considerations

Sample Size Determination

Based on a power of 0.8 (alpha 0.05) to detect superiority of the LILESI group, assuming positive response rates of 45% for the TFESI group and 70% for the LILESI group, we would need a total of 116 patients (57.5 patients in each arm). This sample size would also give us a power of 0.99 to detect non-inferiority (i.e. equivalence between TFESI and LILESI) (non-inferiority margin 0.1).

Patient Outcome Analysis

A reduction of 2 points from baseline on the NRS will be considered a positive response (clinically meaningful or moderate improvement per IMMPACT consensus statement) (15). Primary Endpoint (average NRS over the past 24 hours at 2 months time point): We will apply a difference test and a non-superiority test for binomial proportion to test the primary endpoint. Secondary Endpoints: The secondary endpoints will be analyzed using a test for difference in binomial proportions or a t-test for binomial or semi-continuous variables, respectively.

Interim Data Analysis

An interim analysis will be performed of the first 58 patients by the biostatistician (co-investigator). All study participants, assessors, and other personnel (including other co-investigators) will remain blinded. Safety and efficacy will be evaluated using an O'Brien–Fleming stopping rule of $p < 0.001$ for the interim analysis in order to evaluate for early evidence of treatment efficacy (26).

Crossover, Withdrawal, or Missing Data

We will employ an intention-to-treat (ITT) analysis for this trial (27). Patients that crossover between study arms, withdraw from the study, or for whom there is missing data will all be handled in the same manner. A conservative approach will be taken and we will assume that the patient will receive no further benefit from the study injection. As such, the most recent available outcomes data will be extrapolated to all later time points for which no data are available.