Statistical Analysis Plan

Epidural Steroid Injection with Supplemental Oral Eplerenone for Low Back Pain: A Prospective, Double Blind Randomized Trial

Principal Investigator: Timothy Burroughs

Project Sponsor: Department of Anesthesiology, University of Cincinnati College of Medicine

UC IRB Number: 2017-2713
IRB Approval Date(s): 10/11/2017

SAP Date (PI Signature Date): 1-17-18
Version: Original
Statistician(s): Judith A Strong

This SAP has been reviewed and approved by:

Timothy Burroughs, Principal Investigator — Date: 1-17-2018

Judith A. Strong, Statistician — Date: 1-17-2018

A. Introduction:

Low back pain is a leading cause of disability and health care costs in the United States, and treatments are ineffective for many patients. Epidural steroid injections are a common treatment, but their efficacy has been questioned and for many patients they do not provide complete relief. We hypothesize, based on preclinical studies, that lack of complete efficacy may be due to the fact that clinically used steroids activate not only the intended drug target, the glucocorticoid receptor (GR), but also the pro-inflammatory mineralocorticoid receptor (MR). To test this hypothesis, this pilot study will recruit patients scheduled for lumbar epidural steroid injections for degenerative disc disease, and randomize them to receive a concurrent treatment with oral eplerenone (a clinically approved antagonist of the mineralocorticoid

receptor) or placebo for 10 days starting just after the epidural injection. The primary outcome will be improvement in treatment outcome as measured by the Oswestry Low Back Pain Disability Questionnaire, a validated research instrument that investigates both pain and functional outcomes. Subjects will be followed for one year. Secondary outcomes include the clinical course, in particular, whether the patient requires additional injections or not as part of their routine clinical care.

B. Specific Aims and Hypotheses

Aim 1: Test the hypothesis that subjects receiving eplerenone will show greater improvement in the Oswestry Low Back Pain Disability Questionnaire 12 months after the epidural steroid injection than subjects receiving placebo (primary outcome measure).

Aim 2: Test the hypothesis that subjects receiving eplerenone will show greater improvement in the Oswestry Low Back Pain Disability Questionnaire at earlier time points (2 weeks, 3, and 6 months after the epidural steroid injection) than subjects receiving placebo.

Aim 3: test the hypothesis that subjects receiving eplerenone will have better clinical outcome of their epidural steroid injection than subjects receiving placebo.

C. Study Design

The University of Cincinnati Department of Anesthesiology has two suburban pain clinics that will serve as sources for recruiting subjects, UC Health Pain Medicine Center (Midtown) and UC Health Pain Medicine Center (West Chester).. Our target number for study enrollment is 40 subjects (20 per group). We have obtained authorization for 60 subjects, in order to allow for subjects who drop out. Patients evaluated for degenerative disc disease are routinely given an epidural steroid injection as part of their treatment regimen. Often this is the preferred treatment; if there is no clear indication for surgical intervention, a more conservative approach is sought prior to considering surgery.

Eplerenone and placebo pills with blinded labels will be provided by Investigational Drug Pharmacy. We will use a block-stratified randomization schedule with blocks of sizes 2 and 4. The West Chester and Uptown locations will have separate randomization schedules. Patients will be randomized to receive either eplerenone or placebo, which will be taken for 10 days starting two days after the epidural injection. The dose of eplerenone will be 50 mg PO daily. Eplerenone is extensively metabolized with less than 5% excreted unchanged in the urine. Thus, renal dysfunction has little effect on eplerenone pharmacokinetics. However, patients with compromised renal function may be at greater risk for hyperkalemia when taking eplerenone. For this reason, a blood sample will be obtained from each participant to verify inclusion criteria related to kidney function (see below) based on a basic metabolic panel performed the day of the procedure. Subjects with elevated potassium or creatinine will not be included in the study. The blood sample will be obtained just prior to the epidural injection, at the clinical laboratories located within (West Chester site) or adjacent to (Midtown clinic) the participating pain clinics. This will allow the results (metabolic panel including K+ and creatinine level) to be available by the following day. In order to avoid having subjects make an additional trip to the clinic, subjects will receive their study medications via overnight delivery service, once their blood test

results have been reviewed. Alternatively, subjects who prefer may return to the clinic to pick up their medications. A single take-home sheet of information about the study medication will be given to each patient along with the medication, to help reinforce these directions. We anticipate that few subjects will be excluded on the basis of their blood test.

Patients are normally seen for follow-up approximately one month after an epidural injection. Subjects who are recommended to have a second epidural injection at this follow-up visit will receive a second dose of the same study medication they received after their first injection. The same protocol will be followed: such subjects will have a repeat blood draw and re-confirmation of inclusion parameters prior to restarting the medication. Subjects who become ineligible at the time of the second injection will not receive a second round of study medication, but will continue to complete questionnaires and their data will be retained for analysis.

All patients will receive the same epidural steroid and approach (interlaminar injection of Kenalog (triamcinolone) and saline) as part of their standard care. Triamcinolone has a substantial potency for the MR in addition to the GR; all of the steroids commonly used for epidural injections show some activity at the MR. The procedures and drug are routinely used at the participating clinics for treatment of degenerative disc disorders.

We will use the REDCap (Research Electronic Data Capture) system for secure web based capture of questionnaire data, which is required in order to protect the confidentiality of the subjects' data.

Inclusion criteria::

- Adult patients of either sex, age 18 to 65
- Scheduled for lumbar epidural steroid injection as part of routine clinical care
- Have a diagnosis of lumbar degenerative disc disease demonstrated on either lumbar X-Ray or lumbar MRI.
- Have unilateral radicular symptoms or electromyograph consistent with radiculopathy and exam findings corresponding to this diagnosis: with symptoms reflecting a dermatomal distribution of pain and positive response to straight leg raise test, which is known to be a sensitive, but not specific test for nerve root irritation.

Exclusion criteria: Excluded from the study will be patients with medical contraindications, including specifically those related to use of eplerenone:

- Unable to complete questionnaires or give informed consent in English
- Unavailable for follow-up contacts to complete questionnaires
- Renal impairment (estimated glomerular filtration rate (GFR)<50 mL/min or serum creatinine >1.8mg/dL) on metabolic panel obtained just prior to epidural injections.
- Elevated serum potassium (>5.5 mEq/L) on metabolic panel obtained just prior to epidural injections.
- Have undergone previous lumbar surgery.

- Treated with oral steroids or injectable steroid within the past year.
- Diabetic
- Systolic blood pressure reading less than 100 mm Hg at most recent clinic visit.
- Prescribed protease inhibitors, a class of antiviral drugs widely used to treat HIV/AIDS and Hepatitis C.
- Taking strong CYP3A4 inhibitors
- Taking potassium supplements or potassium-sparing diuretics (amiloride, spironolactone, or triamterene) or using salt substitutes that contain potassium
- Lactating.
- Pregnant

.

D. Statistical Analysis Plan

For categorical variables, counts and percentages will be presented. As a check on randomization, groups will be compared using the Fisher's exact test. For continuous variables, mean, median, standard deviation (SD) and inter-quartile range (IQR) will be presented. Groups will be compared using the t-test, except that non-parametric methods will be used for ordinal variables or variables distributed non-symmetrically.

D1. Aims 1 and 2:

Each Oswestry response has 6 ordinal response choices scored 0 through 5. With 10 items and with the lowest score (0) representing the least disability, the total raw score ranges from 0 to 50. The score is expressed as a percentage of the maximum possible score. If a subject omits one question, the percentage score is based on a maximum score of 45. If a subject omits more than one question the questionnaire is considered invalid and the data not used. Improvement scores are calculated by subtracting the score at a given time point from the score obtained prior to the first epidural steroid injection. Group differences in the improvement scores at the 12 month time point and at the intermediate time points will be analyzed using the Mann-Whitney test.

Patients who are withdrawn from the study due to the initial blood test results will be considered as screening failures; no follow-up data or questionnaire scores will be obtained.

D2. Aim 3: The clinical outcome of the first epidural steroid injection will be abstracted from the medical chart record of the follow-up visit that occurs approximately 1 month after the injection, and will be summarized as an ordinal variable scored as: 1 adequate pain relief, no further treatment recommended; 2, partial relief, second injection recommended; 3 little pain relief, alternative treatment recommended.

Demographic data will be compared between the groups to determine if values differ significantly despite randomization (table 1 below).

E. Variables in the analysis data set

Patient unique ID
Age at first epidural steroid injection (years)
Date of epidural steroid injection
Weight and height at time of epidural steroid injection
Date of enrollment
Gender
Race
Ethnicity
Randomized to control or experimental group?
Oswestry scores (prior to first injection, 2 week, 3, 6, and 12 month post first injection)

F. Variables to Create / Calculate

BMI
Change in Oswestry score (score at each time point minus baseline score)

G. Data Sources

- EPIC chart review
- Oswestry scores exported from REDCap (baseline, 2 week, and 3, 6, and 12 month after first epidural steroid injection)

H. Software Used (with References) and Specialized Macros (with References)

Calculation of basic statistical parameters, t-tests, Mann-Whitney tests, and Fischer's exact test will be conducted using GraphPad Prism (GraphPad Software, Inc.) or SAS 9.4 (SAS Institute).

I. Mock tables to be produced

Table 1: Descriptive table of demographics of experimental and control groups prior to intervention.

Description	Control (N = ***)[1]	Experimental (N = ***)[1]	p value
Age at time of first injection (years)			
Weight at time of first injection			
Height at time of first injection			
BMI at time of first injection			
Race			
Ethnicity			
Oswestry score at first injection			

[1]Mean, SD, median, interquartile range for continuous variables, number and % per group for categorical variables.

Table 2 Pain and disability outcomes

Description	Control (N = ***)	Experimental (N = ***)	p value
Change in Oswestry score at 2 weeks after injection			
Change in Oswestry score at 3 months after first injection			
Change in Oswestry score at 6 months after first injection			
Change in Oswestry score at 12 months after first injection			
Clinical outcome of first injection[3]			

[3] Converted to ordinal scale 1 – 3