Post-lesion Administration of Dexamethasone to Prevent the Development of Neuritis After Radiofrequency Ablation

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JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Chronic neck and back pain has become one of the leading causes of disability and loss of productivity. For many patients with facet- or sacroiliac joint-mediated pain who have responded to diagnostic nerve blocks, radiofrequency ablation of the nerves innervating the joints can provide long-term relief. Radiofrequency ablation (RFA) is a relatively safe procedure with minimal risk of adverse events. However, with any procedure involving damage to the peripheral nervous system, there is risk of post-procedure neuropathic pain. Following both lumbar facet joint RFA, and sacroiliac joint RFA, post-ablation neuropathic pain (PAN) has been documented at a rate ranging from 0.5% to 9.2% per lesion, and can last several weeks, resulting in a decrease in quality of life during this time period.

Transforaminal epidural and intra-articular steroid injections are commonly used in interventional spine procedures to decrease the inflammation at the nerve root or the facets, and pain relief. Therefore, we will test the hypothesis that dexamethasone injection delivered at the time of lesion effectively prevents the development of PAN through a placebo-controlled, double-blind, randomized, multi-center trial in patients undergoing cervical, thoracic, lumbar, and sacroiliac joint radiofrequency denervations.

2. Objectives (include all primary and secondary objectives)

- Primary: To determine if the immediate administration of dexamethasone to the post-ablation site diminishes the incidence of post-ablation neuropathic pain
- Secondary: Stratify cervical vs. thoracic vs. lumbosacral data points to compare if post-ablation neuritis is dictated by anatomical location. Also look at the gauge of the needle used in each patient and radiofrequency parameters to see if associated with neuritis incidence. We will track level of disability and effectiveness of ablations with completion of Oswetry Disability Index and/or Neck Disability Index at baseline, 4 weeks, and 8 weeks after completion of bilateral ablations.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Chronic neck and back pain has become one of the leading causes of disability and loss of productivity. This is often associated with poor quality of life, depression, anxiety, and sleep disorders. Conservative measures, such as physical therapy and medications are first-line treatment options and provide improvement of pain in some patients. However, for those who are not responsive to conservative management, interventional procedures are another treatment option. For many patients with facet- or sacroiliac joint-mediated pain who have responded to diagnostic nerve blocks, radiofrequency ablation of the nerve innervating the joints can provide long-term relief. Radiofrequency ablation (RFA) is a relatively safe procedure with minimal risk of adverse events.[1] However, with any procedure involving damage to the peripheral nervous system, there is risk of post-procedure neuropathic pain. Following both lumbar facet joint RFA, and sacroiliac joint RFA, PAN has been documented at a rate ranging from 0.5% to 9.2% per lesion. [2]

PAN is described as a burning pain at the level of the ablation. In patients who have undergone lumbar facet or sacroiliac joint radiofrequency denervation, these symptoms can last anywhere from 2 to 6 weeks. [2,3] Unfortunately, the incidence of PAN is higher in patients who have undergone cervical facet radiofrequency innervation. The incidence is reported to be approximately 19 percent, with an average duration of 2.6 months [4] and can drastically affect a patient's quality of life during this time period.

Transforaminal epidural and intra-articular steroid injections are commonly used in interventional spine procedures to decrease the inflammation at the nerve root or the facets, and pain relief. Therefore, we will test the hypothesis that steroid injection delivered at the time of lesion effectively prevents the development of PAN through a placebo-controlled, double-blind, randomized trial in patients undergoing cervical, thoracic, lumbar, and sacroiliac joint radiofrequency denervations.

Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

This is a multi-centered double-blinded prospective clinical trial. Patients will be recruited from the pool of patients seen by Dr. Chhatre in the pain management clinic through the Department of Physical Medicine and Rehabilitation. Patients will be recruited from the pools of patients seen by PIs at our collaborating sites (Cornell/Columbia) in the pain management clinic through the Department of Physical Medicine and Rehabilitation. Candidacy for bilateral ablation will be determined by the standard of care, mainly pain relief >50% after two prior bilateral diagnostic blocks. In routine care, these patients are seen in clinic to discuss the risks and benefits of radiofrequency ablation in a clinic. Once patients are consented, they are brought in for the procedure in 2 to 4 weeks. Patients who were not consented in the clinic will also have the opportunity to enroll in the study on the day of their

procedure. They first receive a unilateral lesion, and are brought back to receive a lesionon the other side in no sooner than one week. Patients will then be followed in the clinic in 4 weeks after the procedure to monitor response. Patients can request an earlier appointment if complications arise. If patents develop PAN, they are either monitored without intervention, or initiated on gabapentin or oral corticosteroids, depending on the severity of their symptoms.

b. In this multi-center study, Johns Hopkins will be the coordinating center. All contributing PIs from our collaborating sites have provided contact information (email, direct phone numbers, and addresses of their respective offices). Each center will be submitting separate IRB protocols at their respective institutions. Once approved they will send us copies of completed documents and consent forms. Although this research is not federally funded (as mentioned later in this protocol) all participating centers will file an FWA with OHRP. Any changes to the protocol will be communicated between sites via secured email to assure all sites have the most current version of the protocol. Data will be collected at each respective site and stored on encrypted servers. The collected data will be shared once enrollment is complete for analytical purposes only. If any events or deviations occur at participating centers, our collaborating PIs have agreed to notify the coordinating center (Johns Hopkins) immediately so we may act in a timely fashion.

   In our study, we will add the following steps:
   - Patients will also be consented for the study at the same time as the time of consent for radiofrequency ablation. If patients choose not to participate, they will continue with routine care.
   - At the time of the unilateral lesion, either steroid (dexamethasone 4mg/mL, with 1mL given at each lesion site) or normal saline (1mL) will be administered at the lesion site as determined by randomization.
   - At the time of lesion on the other side, steroid will be administered at the lesion site if normal saline was given previously on the opposite side, and vice versa,
   - There will be an initial 2 week follow up asking exclusively about development of post-ablation neuropathic pain. At the two post-procedure visits spaced 4 weeks apart, patients will be given a questionnaire that will ask about development of neuritis, and any adverse reactions after the procedure. If neuritis is present, the onset and duration will also be recorded. If neuritis is present, but the level is generalized or unclear, post-ablation neuritis will be recorded at a single level that most closely matches the clinical presentation. The questionnaire will then be scanned into the patient chart, and reviewed by co-investigators when data collection occurs. Repeat ODI and/or NDI will be filled out at these follow ups to track efficacy of ablations. If patients cannot be seen in clinic at the 4 week or 8 week follow up, co-researchers will follow up with patients by phone.

c. Study duration and number of study visits required of research participants.

- Patients will be enrolled in the study for approximately 3 months, and will be seen at a total of 4 visits - 1 pre-ablation visit 1 month prior to the procedure, for the procedure itself, and post-ablation for 2 visits spaced 4 weeks apart. There is also a 2 week telephone follow up exclusively assessing incidence of PAN. The study itself will take place over a period of 2 years in order to enroll enough patients to have an adequately powered study.

d. Blinding, including justification for blinding or not blinding the trial, if applicable.
   - This trial will be double blinded to ensure that there is no bias on the part of the provider performing the procedure or seeing the patient in follow up, or on the part of the patient when reporting outcomes
   - Patient is seen in clinic by either the nurse practitioner, fellow, resident, or Dr. Chhatre (the same applies to collaborating sites and respective PIs) and is identified as needing bilateral ablations of the cervical, thoracic, or lumbar facets, or sacroiliac joints, and is consented for the study.
   - As part of routine care, the provider that saw the patient then notifies the secretary of the procedure that is needed. Information will also be included that the patient is eligible for the study. Subsequently, the secretary will call the patient to set up procedure dates. The same process is to be conducted at our collaborating sites.

   - The procedure schedule will be sent to Dr. Chhatre (or respective collaborating PIs) and the research team members the night before procedure day with the scheduled patients. Patients in the study will be marked on this schedule.
   - The research team adds the eligible patients to a separate list that is sent to an un-blinded co-investigator with directions on which side to inject dexamethasone or normal saline based on randomization

e. Justification of why participants will not receive routine care or will have current therapy stopped:
   - Not applicable. All patients in this study will continue to receive routine care, through scheduled ablation procedure and continuation of established medication regimen for pain management.

f. Justification for inclusion of a placebo or non-treatment group.
   - A placebo group is present to compare the current standard of care and the addition of our intervention and to ensure that any changes are the not the result of the experimental paradigm (i.e. active injection post-lesion).

g. Definition of treatment failure or participant removal criteria.
   - Treatment failure is defined as the presence of post-ablation neuropathic pain in the period up to 2 months after post-ablation steroid administration.
   - Participant removal criteria:
     - at patient request for removal

- development of immediate onset of weakness or sensory changes post-injection. At that point, the patient will not be given further injections, but data will be used to report an adverse event
- lack of post-procedure follow up
- Any additional procedures that include additional steroid administration

h. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
- Patients will continue with routine care when the study ends or if their participation in the study ends prematurely. They will be continued to be followed at the pain clinic, and if are determined to need subsequent radiofrequency ablations after the participation in the study, these will be done routinely without administration of post-ablation dexamethasone or normal saline.

4. Inclusion/Exclusion Criteria

- Inclusion:
  - patients followed in the pain management clinic in the Department of Physical Medicine and Rehabilitation who are followed by Dr. Chhatre and PIs from collaborating sites.
  - patients with a diagnosis of either cervical, thoracic, or lumbar facet or sacroiliac joint pain who have responded to medial branch blocks and are already scheduled for bilateral radiofrequency ablations
  - age greater than 18 years old
  - English speaking
- Exclusion:
  - not previously scheduled for radiofrequency ablation of the cervical, thoracic, or lumbar facets, or sacroiliac joints
  - Recent systemic or local corticosteroids in the last 3 months
  - on anticoagulation
  - have a pacemaker
  - age less than 18 years old
  - non-English speaking

5. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.
- Dexamethasone is a well-known anti-inflammatory medication that is often used in transforaminal epidural steroid injections and intra-articular facet injections. The dose of dexamethasone is 4mg/mL, with 1 mL given at each level. PAN is caused by inflammation due to the nature of the procedure. The rationale behind dexamethasone pre-treatment is that the inflammatory response would be blunted and subsequent pain would be reduced or eliminated.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

- Dexamethasone has a well-known safety profile. The medication will be used at doses that are currently used in routine spinal corticosteroid injection procedures. The only difference is that the dose will be given after radiofrequency ablation at each lesion site.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.: N/A

6. Study Statistics

a. Primary outcome variable.
   - Presence of post-ablation neuritis at each lesion site

b. Secondary outcome variables: none

c. Statistical plan including sample size justification and interim data analysis.
   - A McNemar's Test will be performed to compare the incidence PAN in the placebo and treatment groups
   - As the most important outcome measure is the nominal measure of whether neuropathic pain develops after ablation, we will collect dichotomous data (neuritic vs. no-neuritic pain). We will perform McNemar's Test to test for a difference in proportions across paired samples (each patient providing his/her own control through unilateral injections of steroid and placebo-saline into each side). We will consider a p-value of less than 0.05 as significant.
   - We will collect a total of 732 samples, where each sample is nerve(s) lesioned on one side; i.e. for a patient receiving a two-level ablation bilaterally, the patient will provide a total of two samples (one experimental-steroid, one placebo-saline). Because we will only collect data from patients with bilateral injections, each acting as his/her own control, the total 732 samples will be comprised of 366 participants for each experimental/placebo condition. We plan to enroll 120 patients at Johns Hopkins and 246 from our collaborating sites in order to get total of 366 participants for each experimental/placebo condition.
   - The sample size was derived through a power-analysis calculation using G*Power Software (ver. 3.1; Heinrich-Heine Universitat). Specifically, an *a priori* test was performed for the McNemar test with a power of 0.8 and significance level of 0.05. Based on available literature (CITE), we determined that baseline incidence of neuropathic pain is 5%, and further determined that a desirable effect size is a minimum of 50% decrease in incidence with steroid injection (overall incidence of 2.5%). With these values, the contingency table showed an odds ratio of 0.487, and the probability of discordant pairs was 0.0725, leading to a total sample size of 732 (actual power 0.82).

d. Early stopping rules.
   - study will also be terminated if there appears to be greater than expected (>10%) incidence of PAN in the treatment group during interim analyses

7. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.
   - Radiofrequency ablation of cervical, lumbar, or thoracic facets or sacroiliac joint

        - major risks: dural puncture, spinal cord injury, hematoma formation, infection. These are exceedingly rare with no cases reported in the literature to date. [5]
        - minor risks: pain at injection site (0.5% frequency), and neuritis (0.5% to 19%), vasovagal reaction (1%)[3,6]
    - Administration of steroids at the lesion site
        - major risks: infection, spinal cord injury are exceedingly rare. Reports are limited to a few case studies. In a large study by El-Yahchouchi et al. in 2016, showed with no reported incidences.
        - minor risks: flushing, headaches (2.6%). [7], increased blood glucose

b. Steps taken to minimize the risks.
    - the procedure will be performed in a sterile fashion under fluoroscopic guidance to decrease the risk of infection, spinal cord injury, and dural puncture. Patients who are anticoagulated will not undergo the procedure. Only non-particulate steroids, such as dexamethasone, will be used to decrease the risk of spinal cord injury.

c. Plan for reporting unanticipated problems or study deviations.
    - any unanticipated problems or study deviations will be reported immediately to the PI, who will then notify the IRB. Enrollment in the study will be stopped at that point until adjustments to the protocol can be made.

d. Legal risks such as the risks that would be associated with breach of confidentiality.
    - As the proposed study does not involve collection or usage of information regarding sensitive materials, such as alcohol or drug use, illegal activities, sexual activity, or mental illness, potential breach of confidentiality does not pose large legal or societal risks. Patients will be de-identified through the assignment of subject ID numbers. The study team will take strong precautions to prevent any possibility of such breach by storing all data on encrypted servers and storing all hard copies of patient sensitive materials in the PIs' offices

e. Financial risks to the participants: none

8. Benefits

a. Description of the probable benefits for the participant and for society.
    - Positive findings, that administration of steroids following ablation significantly reduces incidence of PAN, would cause a non-trivial decrease in unnecessary suffering from a large number of patients undergoing such procedure. Further, the decreased incidence may encourage patients considering such procedures following treatment failure with conventional therapy to undertake the ablation, which is extensively known to provide relief.

9. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

- There will be no compensations for participation in the study, nor will there be penalties for not completing the protocol

10. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

- as all participants of the study would have been scheduled for radiofrequency ablation prior to inclusion in this study and is part of routine care, the cost of this procedure will be covered in the standard fashion through insurance and patient coverage
- patients will be not billed for the cost of the dexamethasone. The cost of this will be covered by the Department of Physical Medicine and Rehabilitation

References:

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[6] Carr CM, Plastaras CT, Pingree MJ, Smuck M, Maus TP, Geske JR, et al. Immediate Adverse Events in Interventional Pain Procedures: A Multi-Institutional Study. Pain Med 2016:pnw051. doi:10.1093/pm/pnw051.

[7] El-Yahchouchi CA, Plastaras CT, Maus TP, Carr CM, McCormick ZL, Geske JR, et al. Adverse Event Rates Associated with Transforaminal and Interlaminar Epidural Steroid Injections: A Multi-Institutional Study. Pain Med 2016;17:239–47. doi:10.1111/pme.12896.