Using Inflammatory Biomarkers and EMO results to Predict Epidural Injection Response in Patients Diagnosed with Lumbar Stenosis

Clinical Study Protocol

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TITLE / MAIN QUESTION

Do inflammatory biomarkers and needle electromyography (EMG) findings have independent predictive ability to identify patients with lumbar spinal stenosis and neurogenic claudication who are more likely to benefit from epidural steroid injections?

BACKGROUND & SIGNIFICANCE

Lumbar spinal stenosis is a common cause of back pain and mobility impairment in older adults [1]. It is often a multifactorial condition resulting from degenerative changes in the spine, and may result in severe disability, with symptoms of lower back pain and/or pain, numbness and weakness of the lower extremities that are often exacerbated by walking and/or standing [2]. Since lumbar spinal stenosis mostly stems from slowly progressive degenerative changes, symptoms often worsen over time, leading to poor health outcomes and high rates of healthcare utilization.

Epidural steroid injection (ESI) with anti-inflammatory compounds such as glucocorticoids is commonly provided to alleviate pain from neurogenic claudication in spinal stenosis: it is estimated that 25% of ESIs performed in the Medicare population and 74% of ESIs in the Veterans Affairs system are for spinal stenosis [3,4]. However, one recent, large, multi-center, randomized controlled trial (RCT) demonstrated no significant benefit of epidural corticosteroids in alleviating symptoms of spinal stenosis [2]. In this study, Friedly et al. conducted a doubleblind, RCT comparing patient outcomes with epidural injection of glucocorticoid plus anesthetic (lidocaine) vs. anesthetic (lidocaine) only [5]. They observed no significant differences at 6 weeks between the two groups of patients with respect to pain-related functional disability or pain intensity. However, a subset of patients who received glucocorticoids plus lidocaine reported significantly higher treatment satisfaction and higher reductions in depressive symptoms [6]. This suggests that ESIs may be effective for a subset of patients with spinal stenosis.

Another treatment modality for spinal stenosis is decompression surgery, which may be effective for some patients but is associated with higher risk especially in the elderly and patients with multiple medical comorbidities. In Davis et al.'s observational study, in a two-year period with 68 patients, 32% of patients opted for surgery, 44% of patients were satisfied with non-surgical management and were discharged after 2 years, but the remaining 24% with non-surgical management (some of whom chose to decline surgery) did not seem to be satisfied with treatment [7]. This study indicates the potential key role that non-surgical management options such as ESIs may play, in some patients. However, better patient selection using indicators or biomarkers for patients who may most likely benefit from ESIs and other non-surgical treatments would be extremely beneficial.

In studying bio-markers that may predict patients' response to ESIs, Scuderi et al. found interferon-gamma (IG) levels to have high predictive value for patients with lumbar nerve root irritation [8], while Golish et al. and Smith et al. found fibronectin-aggrecan complex (FAC) levels to have high predictive value for patients with herniated nucleus pulposus (HNP) [9, 10].

In addition, many other factors (such as lower age and higher education) have been found to predict better outcome for radiculopathy [11]. In particular, needle electromyography (EMG) has been shown in several studies to be a strong predictor for response to lumbar epidural steroid injection (LESI) and transforaminal epidural steroid injection (TFESI) for patients with lumbosacral radiculopathy (LSR) [12-14]. Inspired by these studies, we would like to explore if certain bio-markers such as IG & FAC along with EMG findings can help us predict which patients with spinal stenosis and neurogenic claudication will optimally benefit from ESIs.

METHODS

Subject Recruitment: Recruit 10 adults (who can read English and complete assessment instruments) referred to the UT Southwestern Spine Clinic aged 18 years or older with mildsevere lumbar central canal stenosis identified by Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT) scan, who have symptoms consistent with neurogenic claudication such as pain, weakness, and/or numbness triggered by standing or walking and relieved by sitting. Exclude patients with cognitive impairment; clinical co-morbidities interfering with data collection; severe vascular, pulmonary, or coronary artery disease that limits ambulation; spinal instability requiring surgical fusion; severe osteoporosis; metastatic cancer; excessive alcohol consumption or evidence of non-prescribed or illegal drug use; pregnancy; concordant pain with internal rotation of the hip; active local or systemic infection; abnormal coagulation; allergy to local anesthetic, steroid, or contrast; previous lumbar spine surgery; prisoners; epidural steroid injection within previous 6 months; rheumatologic disorders such as rheumatoid arthritis, psoriatic arthritis, and systemic lupus erythematosus.

Study procedures: Once enrolled, all of the patients will undergo routine sensory and motor nerve conduction studies with EMG and blood tests. Afterwards patients will be scheduled to undergo an ESI of steroid (dexamethasone) under fluoroscopic guidance at or below the level of the suspected pathology. Prior to the injection, a maximum of 3 ml of normal saline will be injected into the epidural space, and aspirated shortly thereafter, and sent for specified inflammatory laboratory tests. The ESI will then take place as per standard procedure. Independent clinical variables will be assessed at three time points including at the initial visit, at 1 month, and 2 months after the ESI. Additional measures used will include the pain disability questionnaire (PDQ), the Swiss Spinal Stenosis Questionnaire, and Numerical Rating Scale (NRS) for back and leg pain.

Lab Collections for Inflammatory Lab Tests: Complete blood count, High sensitivity CRPs (hsCRPs). Bio-Plex Pro Human Cytokine 27-plex Assay, 1x96: coupled magnetic beads, detection antibodies, standards, assay buffer, wash buffer, detection antibody diluent, streptavidin-PE, filter plate, sealing tape, standard diluent, sample diluent for the detection of IL-1beta, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17, eotaxin, basic FGF, G-CSF, GM-CSF, IFN-gamma, IP-10, MCP-1 (MCAF), MIP-1alpha, MIP-1beta, PDGFBB, RANTES, TNF-alpha, VEGF.

SPECIFIC AIMS & HYPOTHESES

Specific Aim 1: Identify biomarkers that can predict if patients will experience significant pain relief and/or improvement of quality of life following ESI, defined as minimum of 30% improvement in pain and/or PDQ scores.

Hypothesis 1: Since steroids relieve pain mainly through anti-inflammatory effects, patients who have pain caused by inflammation, should have certain associated inflammatory biomarkers in high concentration, which will predict their response to the steroid injection resulting in significant pain relief. Patients who have pain not associated with inflammation, as indicated by biomarker levels will therefore not experience significant pain relief after steroid injections.

Therefore, we hypothesize that patients, who have high levels of specific biomarkers identified in their blood or epidural aspirate, will respond favorably to an ESI and experience significant pain and functional improvement following the ESI.

Specific Aim 2: Identify EMG findings of acute denervation that can predict pain relief from ESI.

Hypothesis 2: EMG findings of acute denervation in leg and/or paraspinal muscles are indicators/markers of abnormal neural activities associated with pain and inflammation, and hence will predict pain and functional improvement from ESI in patients with such EMG findings.

Therefore, we hypothesize that patients, who have EMG findings of acute denervation in leg and/or paraspinal muscles, will experience significant pain and functional improvement following the ESI.

ANALYSIS PLAN: This pilot study of 10 patients will yield preliminary data that will lead to standardizing methods of data collection and inform us for a future RCT that is being planned to follow soon after.

EXPECTED RESULTS AND RATIONALE:

Findings from this pilot study, and data on specific biomarkers including blood tests, epidural aspirate analysis and EMG findings that can predict patients' response to ESI will provide us with preliminary data to inform a fully powered clinical trial. Thus informed, this future RCT will be designed to scientifically evaluate patients' long-term response to ESI, determine appropriate attribution to epidural steroids, and refine our understanding of the predictive capabilities of biomarkers including blood tests, epidural aspirate analysis and EMG findings that can be optimally used for better selection for ESI in patients with lumbar spinal stenosis with neurogenic claudication. Eventually, similar studies like this that seek to find biomarkers to predict steroid effects on health management for a wide spectrum of human pathologies will help clinicians use

steroids more selectively and effectively, and hence reduce healthcare utilization and unnecessary patient care, while optimizing their pain and function.

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