

RANDOMIZED CONTROLLED TRIAL OF LUMBAR TRANSFORAMINAL EPIDURAL STEROID INJECTIONS

Study Design

A blinded randomized controlled trial of lumbar transforaminal epidural steroid injections versus intramuscular saline injections in patients with acute lumbar radicular pain from a disc herniation, applied according to guidelines established by the Spine Intervention Society (SIS)

Background and Significance

To be completed by the project's Principal Investigator (PI).

Hypothesis

Patients undergoing a lumbar transforaminal epidural steroid injection (TFESI) will have greater success with radicular pain relief ($\geq 50\%$ reduction in pain) at one-month post-procedure compared to those receiving intramuscular (IM) saline.

Specific Aims:

1. Compare success rates for lower limb pain ($\geq 50\%$ relief of gluteal, thigh, leg, foot pain) in those receiving a lumbar TFESI vs IM saline.
2. Compare success rates for low back pain ($\geq 50\%$ relief) in those receiving a lumbar TFESI vs IM saline.
3. Evaluate the functional improvement observed in the entire cohort and the subgroups with fair and good response to treatment and determine the correlation between reduction in pain and improvement in function.
5. Determine quality of life outcomes in both the TFESI and IM saline groups.
6. Track analgesic medication use in both the TFESI and IM saline groups.
7. Track duration of pain relief in each group.
8. Track return to work status in each group.
9. Track the need for surgery in each group.
10. Report adverse effects.

Recruitment Process

Preferred: Identification of potential study participants from the research center's interventional and surgical clinics.

Allowed: Response to marketing in local primary care physician clinics, other specialty clinics, and local media.

Enrollment Process

Presentation of study and interview by physician or research coordinator in either the clinic or by phone to screen for study eligibility; determination (screening evaluation) based on inclusion and exclusion criteria; and informed consent (both written and verbal) of qualifying volunteers.

Patients may be compensated for their time and participation upon enrollment and for completion of follow-up intervals. Funding would be limited to compensation to study sites based on enrolled patients only.

Patients who decline randomization may be enrolled as a separate cohort to compare their outcomes at the same time points as the study's enrolled subjects.

Inclusion Criteria:

- Adult patients aged 18-60 capable of understanding and providing consent and capable of complying with the outcome instruments used.
- Lower limb pain (gluteal, thigh, leg or foot) in clear radicular pattern that is greater in severity than axial low back pain.
- Physician assessment that pain is of a radicular quality, i.e., lower limb pain of a lancinating, stabbing, or electric quality (as opposed to dull ache) (Ghahreman et al. *Pain Medicine* 2010; 11: 1149–1168)
- Three-day average numeric pain rating score (NPRS) for radicular pain is $\geq 4/10$ at baseline evaluation.
- Recent MRI (within last 6 months) showing a disc herniation at a segmental level consistent with the clinical features.
- Two interventional or spine physicians have reviewed MRI and clinical data (radicular pattern, exam) and agree on etiology.

Exclusion Criteria:

- Moderate-to-severe fixed/bony foraminal or canal stenosis
- Severe motor deficit
- History of substance abuse
- Inability to comply with instruments for outcome assessment
- Previous surgery at the affected level
- BMI > 40
- Bilateral radicular pain
- Any spondylolisthesis at affected or adjacent level
- Systemic inflammatory arthritis (e.g., rheumatoid, lupus, seronegative spondyloarthritis)
- Prior epidural injections for the current painful episode.
- Addictive behavior, severe clinical depression, or psychotic features
- Possible pregnancy or other reason that precludes the use of fluoroscopy
- Current infection or treatment of infection with antibiotics within the past 7 days
- Medical conditions causing significant functional disability (e.g., stroke, COPD)
- Receiving remuneration for their pain treatment (e.g. disability, worker's compensation, auto injury in litigation or pending litigation)
- Incarceration
- Allergy to contrast media

Outcome Instruments

Baseline Only:

- NIH Minimal Dataset, Task Force on Research Standards for Chronic Low-Back Pain (https://painconsortium.nih.gov/sites/default/files/cLBP_RTf_MinimalDataset-508C.pdf)
 - Demographics
 - Duration of back pain
- Nature of pain (i.e. bilateral, symmetrical, unilateral)
- Duration of symptoms for stratification purposes
- NPRS for leg pain and back pain
- MRI grade of nerve root compression using a validated system (such as used in Ghahreman and Bogduk. Predictors of a favorable response to transforaminal injection of steroids in patients with lumbar radicular pain due to disc herniation. *Pain Med* 2011;12:871-79)

Baseline & Follow-up:

- NIH Minimal Dataset, Task Force on Research Standards for Chronic Low-Back Pain
 - Average NPRS back pain (7-day average)
 - Physical function
 - Depression
 - Sleep disturbance
 - Pain interference with activity
 - Opioid use
 - Employment status
- Analgesic use log
- Ancillary treatment log
- Current NPRS for leg pain and back pain
- Physical examination
- Need for surgery
- EQ-5D
 - Quality of life
- Average NPRS for lower limb pain over the last week

Follow-Up Only:

- Duration of pain relief (duration of > 50% pain relief)
- Global perception of change
- Adverse effects (e.g. post-procedural pain, ataxia, dysethesias, dizziness)

Injection Treatment:

- It is suggested that investigators follow the Ghahreman protocol (*Pain Medicine* 2010; 11:1149–1168) of targeting the affected nerve with a TFESI. This typically implies a TF approach to cover the affected nerve root. For example, for a L4-5 herniation compressing the traversing L5 nerve, the TFESI would target the L5 nerve with a L5-S1 supraneural TFESI. A foraminal disc herniation at L4/5 affecting the exiting L4 nerve root would require a L4/5 supraneural TFESI to cover the

L4 nerve root. If the anatomy precludes safe needle placement with a supraneural approach, an alternative transforaminal approach may be used, such as infraneural. If contrast flow is deemed unsatisfactory at the chosen level, the injectionist may modify the level and intra-foraminal position to cover the affected nerve adequately. Steroid may only be injected at a single level.

- A minimum of 2 ml of contrast shall be injected. Procedural images shall be saved including a minimum of pre-injection AP and lateral, post contrast injection AP and lateral, and an AP “washout” (post steroid injection).
- Injection of dexamethasone according to techniques described in the International Spine Intervention Society’s *2nd Edition Practice Guidelines*. The therapeutic dose(s) and volume(s) must be standardized and specified by the investigator. Investigators must comply with information provided in the latest Society guidelines.
- An injection may be repeated if inadequate response is obtained (pain still $\geq 4/10$) with timing of follow-up questionnaires based on last injection.

Power Analysis

To be completed by project’s principal investigator (PI) to demonstrate the size of the study sufficient to provide acceptable confidence intervals for the anticipated success rates in the different groups. The numbers could be based on the Ghahreman study (*Pain Medicine* 2010; 11:1149–1168.) Investigators to confirm that they perform a sufficient number of TFESI in patients with isolated intervertebral disc herniation to support the expectation of reaching the target enrollment number in a reasonable amount of time.

- Using a success rate of 54% (TFESI) vs 13% (IM saline) from Ghahreman study:
 - o 20 per group for 80% power
 - o 23 per group for 85% power
 - o 26 per group for 90% power
- In the Ghahreman study, the success rates of all non-TFESIs was 15% (CI 8-22%) as opposed to 13% success rate with IM saline.
- A more conservative power analysis could be done (enrolling more subjects) but will be left to the discretion of the PI. The PI should confirm and provide details of the power analysis in support of the target enrollment.

No target enrollment is specified for the non-randomized cohort.

Study Timeline

Baseline:

Participants who meet inclusion and exclusion criteria will be enrolled into the study after consenting to and before receiving a first lumbar TFESI. The baseline examination and all baseline questionnaires will be completed within 2 weeks before lumbar TFESI.

Follow-up:

Follow-up on outcome measures to be done at 1 month (+/- 1 week), 3 months (+/- 2 weeks), and 12 months (+/- 2 weeks). The 12-month follow-up may be a phone follow-up with the intention of capturing the natural history of the disease. The 12-month follow-up is not a primary follow-up point to assess outcomes differences between groups.

Study Protocol

Consecutive patients presenting with acute lumbar radicular pain who meet the above-mentioned inclusion and exclusion criteria and who have provided consent will be enrolled in the study. The target enrollment number is based on a power analysis as noted above. Patients will be randomized to receive either a lumbar TFESI or IM saline. Both groups will receive ongoing equivalent conservative treatments (physical therapy and medications) per the direction of the principal investigator.

Protocol should include a quality monitoring board tasked with reviewing clinical notes documenting inclusion/exclusion criteria and appropriate technique, as well as procedural images of final needle placement in AP and lateral views for every procedure for the purpose of quality control. Options for the quality monitoring board include a group of SIS Research Division and/or Board members on a volunteer basis or a group of approved SIS members. Subjects with sub-optimal images shall be withdrawn from the trial as protocol violations.

Group Assignments:

Patients are randomly assigned by a computerized random number generator program to the active treatment or control groups. The principal investigator should further describe the randomization process.

Blinding:

This is a single-blinded study. Patients will remain blinded to their group assignments throughout the study unless they meet criteria for crossover treatment. The treating physician cannot be blinded and therefore, cannot also serve as the assessing clinician. The assessing clinician will remain blinded as to the patient's treatment group and collect outcome measures. Care should be taken to ensure that the patient remains blinded to the procedure, especially if blinded to the placebo group. For example, the procedures could take place as follows: in every patient, the physician shall place the needle into the target position for the TFI. Before injecting anything, the nurse consults the randomization schedule. By a hand signal not in view of the patient the nurse points down if the allocation is for TFESI but points up if the allocation is IM saline. If the allocation is IM saline, the physician gently withdraws the needle to an intramuscular depth, injects contrast medium, then injects saline. Under this protocol, three films must be kept: the needle in position for TFESI, the needle withdrawn, and after the IM saline contrast medium.

To help determine the blinding success in this study, patients should be asked after their procedure if they believe that they received the active treatment, the placebo, or if they could not sense to which group they were assigned.

Crossover:

Patients will be assessed 7-10 days after their allotted treatment. If patients still have significant pain ($\geq 4/10$ on the NPRS), they will be offered a repeat of the allocated treatment (TFESI or IM saline). After one month, participants in the IM saline group will be allowed to cross over and receive a TFESI (rescue treatment) if pain remains severe. Any patient who crosses over would be considered a treatment failure. Any patient undergoing surgery would be considered a treatment failure as well.

Injection:

This study will investigate lumbar transforaminal injections of steroid. The intervertebral level of the injection will be determined by the treating physician based on 1) clinical presentation (distribution) of their pain and 2) and the location of the patient's disc abnormality seen on advanced imaging.

Co-interventions:

Both groups may receive ongoing equivalent conservative treatments (physical therapy and medications) as per the direction of the principal investigator. Any treatments related to the participant's spine condition will be reported.

Primary Outcomes:

1. Success rate for lower limb pain (gluteal, thigh, leg, foot), specifically defined as $\geq 50\%$ reduction in pain from baseline to 1-month post-procedure.

Secondary Outcomes:

1. Success rate and duration of low back pain, specifically defined as $\geq 50\%$ relief of low back pain.
2. Physical function
3. Health-related quality of life
4. Pain interference with activity
5. Health-care utilization for back pain
6. Need for surgery
7. Work status

The same outcomes will be tracked in the cohort who did not agree to be randomized but did agree to have their outcomes tracked.

Data Management

Data will be collected on standardized case report forms and entered into a HIPAA-compliant electronic database (e.g. Microsoft Access) that provides an appropriate interface with a robust statistical package (e.g. SPSS). All study-related hard copy materials will be stored in locked file cabinets.

Analysis

Overall success will be calculated for both groups by determining the proportion of participants with $\geq 50\%$ relief of index pain at 1 and 3 months for lower limb pain. Success rate again will be determined for low back pain ($\geq 50\%$ relief). These are all dichotomous outcomes that allow for categorical data analysis.

Secondary outcomes will be similarly evaluated. Function and quality of life will be evaluated in the treatment group compared to the control group at the 12-week follow-up. Also, the percent of subjects who are not taking opioids or partial opioids will be categorized as well as return to work status. Need for surgery will be a simple "yes" or "no" answer.

Duration of relief by each individual participant will be graphed using a life table analysis specifically documenting how long each subject maintained at least 50% pain relief. Quality of life measures (EQ-5D) will be descriptive.

Analysis shall be performed to determine the association of outcomes in relation to degree of nerve root compression. In addition, a kappa score will be calculated for agreement among the blinded readers determining degree of nerve root compression.

The proportion of patients from the study sites who were eligible for the study but declined to participate may also be analyzed as an open cohort for comparison to study subjects as well as to document the implementation challenges associated with randomized controlled trials in this field. At a minimum, the number of patients who were eligible but did not participate should be noted.