

Study Design: Prospective Randomized Double Blind Controlled (Explanatory or Pragmatic) Clinical Trial of Intradiscal Therapy “X”.

Background and Significance

To be completed by the project’s Principal Investigator (PI). This should include the rationale for the proposed intradiscal treatment for a prospective explanatory or pragmatic randomized controlled study design.

Hypothesis

A significantly greater proportion of those in the treatment group will have improved pain and function compared to the control procedure (placebo or sham, such as placement of a needle into a region simulating disc access with or without a placebo injectate) group at 6 months and 12 months follow-up.

Specific Aims:

1. Compare the proportion of participants in the treatment group vs. control (placebo/sham) group who respond to treatment by exceeding pre-determined thresholds for improvement (\geq 50% relief of pain by NPRS; between 20-50% relief of pain by NPRS; and less than 20% relief of pain by NPRS in pain and function at 1, 3, 6, 12, and 24 months.
2. Evaluate the functional improvement observed (by ODI) in the entire cohort and subgroups determined by response to treatment, and determine the correlation between reduction in pain, improvement in function, and duration of response.
3. Compare patient characteristics between response groups.
4. Report adverse effects.

Recruitment Process

Preferred: Identification of potential study participants from the research center’s clinics and schedules. Marketing in local primary care physician clinics and social and local media may also be necessary.

Enrollment Process

To be completed by the project’s PI. Include specific details regarding the investigative team and the process for screening, enrollment, and blinding of participants.

Power Analysis

To be completed by the project’s PI to demonstrate that the size of the study is sufficient to provide acceptable confidence intervals for the anticipated success rates in the different groups.

Randomization and Blinding Procedure

To be completed by the project’s PI to demonstrate that appropriate and effective measures are in place to ensure that the desired randomization and blinding occurs. Investigator should outline the unblinding procedures that will be followed for crossovers.

Inclusion Criteria:

- Adult patients aged 18-70 years capable of understanding and providing consent in English (or language of region where research is being conducted) and complying with the outcome instruments used
- Primary pain complaint is axial lower back pain (index pain) for greater than or equal to 6 months

- 3-day average numeric pain rating score (NPRS) for index pain (IP) of at least 5/10 at baseline evaluation
- Patient consents to treatment with intradiscal therapy in a shared decision-making process with the treating physician.
- The participants will have failed conservative care (e.g., 2-3 months of physician-directed medications, physical therapy, massage, home exercises, chiropractic care, and/or modification of activity).
- Other common sources of low back pain will have been ruled out. Lumbar z-joint pain should be ruled out through fluoroscopically-guided medial branch blocks. Sacroiliac joint (SIJ) pain should be ruled out (if pain location is below L5) through image-guided diagnostic SIJ intra-articular injections.
- No plans at the time of enrollment to undergo surgery in the following 6 months
- Provocation discography conducted per the International Spine Intervention Society's 2nd Edition Practice Guidelines is positive and consistent with discogenic pain (internal disc disruption) at one disc only. Note that there are pre-trial clinical exclusions for discography such as the height of the disc.

Exclusion Criteria:

- Disc herniation at index level > 3mm A-P dimension
- Disc herniation at index level causing any nerve compression
- Disc height less than 50% adjacent level
- Radicular pain of nerve root or dorsal root ganglion (DRG) origin
- Spondylolysis at index level
- Spondylolisthesis at index level > grade 1
- Scoliosis >20 degrees in lumbar spine
- Central stenosis at index level of < 7mm AP diameter, foraminal or lateral recess neural compression at index level
- Those receiving remuneration for their pain treatment (e.g., disability, worker's compensation)
- Those involved in active litigation relevant to their pain
- Incarceration
- BMI >35 (Investigator should consider ease of access for ease of procedure, radiological safety, feasibility of diagnosis and treatment.)
- Systemic inflammatory arthritis (e.g., rheumatoid arthritis, lupus)
- Addictive behavior, severe clinical depression, or psychotic features

- Possible pregnancy or other reason that precludes the use of fluoroscopy
- Active bacterial infection or treatment of infection with antibiotics within the past 4 weeks
- Unexplained neurologic deficits, progressive motor deficit, or clinical signs of myelopathy
- Medical conditions causing significant functional disability (e.g., stroke, COPD)
- Any other medical condition precluding safe disc access
- Dallas grade 5 annular tear in discogram for index disc
- Those who have undergone a previous surgery or a mechanical or heat procedure at the symptomatic disc (e.g., discectomy, laminectomy, foraminotomy, fusion, intradiscal electrothermal therapy, intradiscal radiofrequency, and/or thermocoagulation)
- Fracture at index level
- Epidural steroid injection within 8 weeks prior to enrollment
- Those who have a history of any prior lumbar intradiscal therapeutic injection procedure (e.g., injection of steroid, methylene blue, dextrose, platelet rich plasma, or glucosamine and chondroitin sulfate)
- Concurrent participation in any other clinical study of an investigational drug or investigational treatment
- Allergy preventing the use of any medication or injectate
- Chronic widespread pain or somatoform disorder (e.g., fibromyalgia)

Outcome Instruments

Baseline:

- Pain History: patient's description of pain characteristics (e.g., burning, electric) and location of pain symptoms; pain diagram; analgesic use log (opioid and non-opioid)
 - o Neuropathic pain: a questionnaire such as the S-LANNS, the self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs instrument
- Demographics
- Medical and Psychosocial History: work history and current status; BMI; smoking history, history of diabetes mellitus; history of rheumatologic or neurologic disease; history of chronic pain condition other than the IP
- Physical Examination: a standardized straight leg raise (described within the study protocol), possible SIJ pain, evidence of neurocompression, neurological deficit consistent with radicular pain

Patient Reported Outcome Measures:

- EQ-5D Health Related Quality of Life questionnaire
- Oswestry Disability Index (ODI)

- Personal goal achievement/COMBI (Stojanovic *et al.* in *Pain Medicine*, 2015; 16: 513-519.)
- Numerical Pain Rating Scale (NPRS) of index pain (current, 3 day or 7 day average)

Radiologic Details:

- Morphology of the disc planned for treatment (Pfirrmann degeneration grade & Fardon classification), absence or presence of HIZ, osteophytes, presence of central or foraminal stenosis (Pfirrmann compression grade and Modic changes)

Follow-up:

- NPRS of index pain (current, 3 day or 7 day average)
- EQ-5D Health Related Quality of Life questionnaire
- Oswestry Disability Index (ODI)
- Personal goal achievement/COMBI
- Work history and current status
- Analgesic use log (opioid and non-opioid)
- Ancillary treatment log, of any treatment related to the underlying condition other than analgesic use (e.g., injections, physical therapy, chiropractic care, acupuncture, ice or heat)
- Physical examination (primary focus is on any neurologic deficit): straight leg raise, evidence of neurocompression, neurological deficit consistent with radicular pain
- Adverse effects (e.g., numbness/paresthesias, infection, lower extremity pain)

Treatment: (detailed description of the intervention)

- Date
- Side(s) and location(s) of treatment
- Sedatives used
- Type of needle used (sharp/blunt, gauge, straight/curved, active tip length)
- Prophylactic antibiotic use (as determined by PI)
- Injectate volume and max PSI, reason for stopping volume (e.g., pain, max volume, PSI, disc leakage)
- Details specific to treatment type, such as biological substance cell count, as applicable

Study Timeline

Baseline:

Consecutive consenting participants who meet inclusion and exclusion criteria will be randomized to active treatment group or control group. Baseline data will be collected per protocol.

Follow-up:

Routine scheduled follow-up will occur at 2 weeks, 6 weeks (+/- 1 week), 3 months (+/- 2 weeks), 6 months

(+/- 1 month), 12 months (+/- 1 month), and 24 months (+/- 1 month) to gather data according to protocol.

The investigator should identify the time point that will serve as the primary outcome analysis of the randomized trial and an intention-to-treat analysis to evaluate for differences in outcomes between active treatment and controls. All subsequent follow-up periods are intended to evaluate long-term clinical outcomes of the intradiscal therapy and will be evaluated with an as-treated analysis.

The investigator should describe the crossover time designation based on the specific treatment administered in order to provide a humane timeframe for crossover to active treatment, but allowing ample time for the treatment effect based upon presumed mechanism of action. Typically, this time frame would be within 3 to 6 months.

The study start date and the outcome assessment timeline will commence on the date of the participant's initial intradiscal therapy or control treatment. The investigator should determine the timeframe during which a participant must remain blinded to assigned treatment. After the proposed timeframe, patients who have failed treatment per the criteria determined by the PI can be unblinded. Those who received active treatment will be considered treatment failures, by definition, and continue on the regular follow-up schedule. Those treated by placebo/sham treatment may opt to cross over to active treatment, and in doing so, will begin a new 24-month follow-up protocol for the active treatment.

This study is intended to monitor outcomes following an intradiscal therapy; the time-point for evaluation will depend on the treatment administered and should be described by the investigator. The time-point for the evaluation of primary outcome may vary depending on interventions (biologics vs. thermal intervention) and should be identified by the PI.

Study Protocol

Design:

A prospective, randomized, double-blind controlled trial with an option for cross-over, possibly 2:1.

Procedures:

All procedures, including disc access, will be performed according to the *International Spine Intervention Society, Practice Guidelines for Spinal Diagnostic and Treatment Procedures (Second Edition)*. Per the standard of care, selection of patients for the intradiscal therapy will be determined by the treating physician based on overall clinical situation including the location of pain, pain referral patterns, and imaging findings. The PI will provide full procedural details including a list of equipment used, needle type, and all treatment medications. Post-treatment clinical assessment should be performed.

All participants will be given a phone number to contact the research nurse or coordinator along with instructions to call if their pain has returned to the extent that warrants consideration of an additional treatment. Immediate and early post-treatment period, the PI and his/her representative will be available 24 hours to answer any urgent questions or concerns related to the procedure. In addition, the PI and his/her representative will be available to answer non-urgent questions between 8 am and 4 pm. Patients will be contacted in the first week with a standardized questionnaire about their symptoms and given a reminder about the 2 week (+/- 1 week) post-treatment follow up. After the 2 week follow up, patients will be reminded of the scheduled follow up times as described above.

Group Assignments:

The subjects who meet the inclusion/exclusion criteria are then randomly assigned to treatment, placebo/sham treatment, or various treatment groups depending on the study design. The specific placebo/sham treatment would be at the discretion of the PI, but could consist of placement of a needle into a region simulating disc access with or without a placebo injectate. For example, the PI may consider placement of needle tip into Kambin's triangle and injection of contrast as a sham procedure. The blinding procedure for the treating physician and/or patients will be followed as developed by investigator. Data are to be collected at 2 weeks, 6 weeks (+/- 1 week), 3 months (+/- 2 weeks), 6 months (+/- 1 month), 12 months (+/- 1 month), and 24 months (+/- 1 month) follow up.

Blinding:

This is a double-blinded study. Patients will remain blinded to their group assignments throughout the study unless they meet criteria for crossover treatment. The treating physician, serving as the outcomes assessor, will also remain blinded. A trained study nurse or assistant not involved in the patient's care will receive the randomization assignment and implement either active or sham treatment. The treating physician's performance of the active and sham treatments will be identical. The intradiscal therapy will be applied to those in the active treatment group, and not to those in the control group. The control procedure shall be performed in as close a manner as possible to the active treatment procedure.

Cross-over

Anytime after the identified follow-up timeframe, any participant not obtaining adequate pain relief can ask to be unblinded and, if in the control group, can opt to cross-over to active treatment. Cross-over should be permitted depending on when the treatment or treatments should take effect, possibly at 3 to 6 months. In doing so, a new follow-up time-period will begin for this patient who is now placed in the active treatment group for the long-term, as-treated outcomes analysis.

Co-interventions:

Attempts should be made to limit co-interventions during the study period, but appropriate care for the patient should never be withheld. Any treatment related to the participant's spine condition will be reported on an ancillary treatment log. Depending upon the nature of the co-intervention, the participant may be deemed a categorical failure.

Primary Outcomes:

The primary outcome for the randomized, double-blind controlled trial is "treatment response" at the identified follow-up period timeframes.

Treatment response is defined by classification into one of the three following categories:

1. 50% or greater improvement in index pain following the intradiscal therapy
2. 20%-49% improvement in index pain following the intradiscal therapy
3. Less than 20% improvement in index pain following the intradiscal therapy

Secondary Outcomes:

1. Function (ODI)
2. Personal goal achievement/COMBI (Pain Med, 2015)
3. Work status
4. Health-related quality of life (EQ-5D)
5. Medications used, continued, or discontinued. MSO4 equivalents, if opiates

6. Other treatments sought or requested

Data Management

Data will be collected on standardized case report forms and entered into a HIPPA-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

Results of the randomized controlled trial will be determined by an analysis of categorical data from the time-point identified by the investigator as the primary outcome measurement time period. At this time-point, and prior to allowing crossover, overall treatment response rates (in the previously defined categories of failed, fair, or good) will be calculated for both active treatment and control groups using an intention-to-treat analysis. For time periods beyond the primary outcome measurement time-point, intention-to-treat and as-treated analyses will be performed with primary reporting based on the as-treated analysis to assess the long-term effectiveness of active treatment.

Subgroup analyses will be performed to assess treatment response and long-term effectiveness in patients reporting $\geq 50\%$ relief from the intradiscal therapy as compared with those reporting between 20-50% relief. Data will also be examined to identify any factors tied to treatment success and need for repeat treatment.

Secondary outcomes will be similarly evaluated. The four patient-specified activities (COMBI) that have been impacted by pain will be categorically analyzed as either resolved, or not. For ODI and EQ-5D the proportions of those achieving and not achieving the established minimal clinically important differences (MCID) will be determined and compared between the active treatment and control groups at the follow-up time-point designated as crossover. For long-term analysis of treatment effectiveness, an as-treated analysis will determine the proportion of patients exceeding these response thresholds.

In addition to these categorical outcomes, changes in group mean scores will be measured and compared, as will health care resource utilization and work status. Correlation between reduction in pain and improvement in function will be evaluated with a regression analysis of changes from baseline to the time frame designated as crossover. Finally, all adverse events will be recorded and reported for both the active treatment and control groups.

Significant and meaningful clinical changes in the NPRS (such as a 3 or greater drop) in the pain score and similar functional improvement in the ODI scores would be considered treatment success. Return to work and activities would be considered a success. A significant decrease or a discontinuation in the medications used with little to no other treatments sought or requested would be considered a success for secondary outcomes. Statistics should be presented to support these findings.