Comparative Effectiveness of Lumbar Transforaminal Epidural Steroid Injections with Particulate versus Non-Particulate Corticosteroids for Lumbar Radicular Pain: a Randomized, Double Blinded Trial.

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Study Design

Part One:

120 individuals that meet inclusion and exclusion criteria and who are scheduled to undergo single level, unilateral lumbar transforaminal epidural steroid injection below L3 level for focal pathology will undergo a double blind trial with either triamcinolone acetonide (Kenalog) or dexamethasone phosphate (Decadron).

After obtaining all appropriate informed consent for the procedure, subjects will be randomized to one of two groups. Each will undergo standard TF ESI by independent physician at level of target pathology as determined by physician after reviewing imaging and completing a history and physical exam (procedure protocol outlined below under study interventions). Physician performing the injection will not be involved in research follow-up or future treatment decisions including decision to repeat injection.

Following the procedure the subject will undergo standard nursing phone follow-up on the next business day that includes assessment of systemic side effects including facial flushing, sleeplessness, and non-positional headaches.

Subject to follow-up in clinic for standard 14-21 day follow-up with blinded physician. Validated outcome measures will include:

Primary Endpoints / Assessment Tools:

10 point Visual Analog Scale (VAS) –Validated Pain Scale
Osweistry Disability Instrument (ODI) –Validated Low Back Functional scale
Short Form 12 (SF-12 v2) –Validated Health and Wellness scale

Secondary Outcomes at 2-3 weeks:

Medication Use (including opioids, anti-inflammatory and neuropathic medications)
Co-Interventions (chiropractic, massage, and physiotherapy)

Work Status

Neurologic Exam

Satisfaction Scale

**Part Two:**

If the subject claims benefit (of any kind) with the first injection they can receive a second/third injection if appropriate and as determined in discussion with the treating physician. Subsequent injections may occur in the 12 months following initial injection. The injecting physician and follow-up physician remain blinded and in the same treatment group. Follow-up occurs after each injection in office at 14-21 days after each injection as well as at 3, and 6 months with a physician. There is a maximum of 3 injections in one year.

Per standard practice procedure if subjects report worsening of symptoms or no improvement of any kind after the lumbar spine TF ESI, they will not be eligible for repeat injections and analyzed as a treatment failure.

**3 Month Follow-up Primary Outcomes:**

- 10 point Visual Analog Scale (VAS) –Validated Pain Scale
- Oswestry Disability Instrument (ODI) –Validated Low Back Functional scale
- Short Form 12 (SF-12v2) –Validated Health and Wellness scale

**Secondary Outcomes at 3 months:**

- Medication Use (including opioids, anti-inflammatory and neuropathic medications)
- Co-Interventions (chiropractic, massage, and physiotherapy)
- Work Status
- Neurologic Exam
- Satisfaction Scale

**6 Month Follow-up Primary Outcomes:**

- 11 point Likert Scale -Pain Reduction scale
Oswestry Disability Instrument (ODI) -Low Back Functional scale

Short Form 12 (SF-12 v2) –Health and Wellness scale

Total Number of Injections received

**Secondary Outcomes at 3 months:**

Medication Use (including opioids, anti-inflammatory and neuropathic medications)

Co-Interventions (chiropractic, massage, and physiotherapy)

Work Status

Neurologic Exam

Satisfaction Scale

**Type of Study:**

Double Blinded prospective randomized controlled trial.

**Randomization:**

The subjects will be randomized into one of two groups in a 1:1 fashion as follows:

The randomized groups will be:

1. Lumbar TF injection with 1.25cc preservative free dexamethasone phosphate (Decadron 10 mg/ml) with 0.75 ml preservative free normal saline -total steroid dose 12.5mg, total injectate volume 2.0 ml

2. Lumbar TF injection with 1.5 cc of triamcinolone (Kenalog 40mg/ml), with 0.5 ml of preservative free normal saline -total steroid dose 60mg, total injectate volume 2.0ml

**Measures Taken to Avoid Bias:**

Subjects will undergo independent randomization.

Physician drawing up and injecting the steroids will not be involved in any of the follow-up assessments for the subjects. The injecting physician will not be involved in any treatment decisions for the subjects, including alternative therapies and decision to re-inject. Therefore the subjects, treating physicians, and
physicians completing the follow-up assessments will be blinded to steroid allocation. The injecting physician will not be blinded to steroid allocation, but will not be involved in any clinical decision making, thus allowing for double blinding.

At end of study an unblinding question will be asked of treating physicians.

**Study Interventions:**

Intervention: All subjects to be treated with a single level transforaminal epidural steroid injection according to the protocol recommended by the International Spine Interventional Society:

- Subject will be consented for procedure by physician performing injection.
- Side to be injected will be identified and marked by injecting physician with using a skin marking pen.
- Subject will be brought into procedure suite after appropriate consents obtained and site identified by registered nurse as part of standard protocol.
- Subject will be placed prone on a fluoroscopy table
- Subject will have continuous monitoring of vital signs including pulse oximetry, blood pressure, and pulse by registered nurse.
- Skin area prepped with betadine solution three successive times to ensure sterility.
- A steriley drape will be placed over the target area.
- Target sight localized with fluoroscopy. The correct level will be identified in the AP view. Then the fluoroscope was positioned to provide an oblique view.
- Skin will be anesthetized with approximately 2 ml of 1% lidocaine (preservative free) administered with a sterile 25 gauge 1.5 inch needle.
- Using fluoroscopic guidance, a sterile 22 gauge 3.5 or 5 inch spinal needle (depending on body habitus) will then positioned at the neural foramen in the superior aspect above the exiting spinal nerve. Precise needle placement will be confirmed by fluoroscopy views including AP, Lateral, and Oblique (just inferior to the pedicle, under the lateral ½ of the pedicle as seen on an AP view).
- Correct placement is the re-confirmed with slow injection of 1-2 ml of radio opaque contrast (Iso-vue 300) under live fluoroscopy through microbore tubing under live fluoroscopy. If intravascular flow is observed the needle will be repositioned. The contrast should spread both peripherally along the nerve root and centrally along the pedicle to the epidural space consistent with an epidural flow pattern. If correct needle placement cannot be confirmed by injecting physician, the procedure will be aborted.
- A test-dose of 2ml of 1% lidocaine is instilled through microbore tubing to ensure lack of inadvertent arterial injection as a second safety measure.
- Subjects will then have 2ml of steroid preparation administered through microbore tubing in accordance with randomization scheme.
- Microbore tubing will then be flushed with 1ml of contrast dye to ensure full delivery of steroid to target area.
- Spinal needle will then be withdrawn
Subject will be escorted to the post-injection waiting area by staff where they are monitored for 15-30 minutes before they are allowed to leave.

**Expected Duration of Subject participation:**

As per standard treatment protocol, after procedure subjects will have standard next business day nursing phone follow-up to include an assessment of systemic side effects including:

facial flushing, sleeplessness, and non-positional headaches.

Subjects will then be asked to follow-up at 2-3 weeks post injection as per standard treatment protocol. Subjects will be asked to follow-up with physician at 3 and 6 months after the last injection, with a maximum of three injections in one year. All subjects will be paid $50 for the first office visit, $100 for the 3 month visit, and $150 for the 6 month visit (with a maximum of $300 per subject upon completing all planned follow-up).

This is intended to reimburse subjects for their extra time required to fill out additional paper work, as well as travel time and parking for extra physician office visits dictated in study protocol.

At end of study participation subjects will be debriefed and informed of the exact steroid compound they received and have their medical records updated accordingly.

**Selection and withdrawal of subjects:**

**Inclusion Criteria:**

1. Subjects ordered to undergo Lumbar spine ESI for lumbosacral radicular pain

2. Lumbar spine imaging (MRI, CT scan, CT myelogram) that demonstrates neural compression that correlates with subject’s radicular pain.

3. Current daily pain less that is less than 6 months (180 days) duration

4. Age over 18

6. Targeted injection level planned for L3 level or lower.

7. English Speaking/Reading
**Exclusion Criteria:**

1. Any illness or disorder that interferes with the safe conduct of the procedure. These might include: allergy to local anesthetics, antibiotics, or radiographic dyes; a tendency to bleed; or an inability to lie still, e.g. because of persistent cough;

2. Litigation

3. Case involving Worker’s Compensation

4. Pregnancy (x-ray guidance is required for procedure, which could result in potential fetal risk)

5. Inability to provide the information necessary to assess the outcome of the treatment.

6. Concomitant, painful conditions, such as knee pain, that might interfere with the subject’s ability to determine the degree of relief of their radicular pain.

7. Prior epidural steroid injections for this current painful episode

**Withdrawal Criteria:**

1. Subject can request withdrawal from study at any time for any reason.

2. Physician can break blinding at any time if deemed necessary for patient care.

3. If subject undergoes spinal surgery at anytime during scheduled study subject will be treated as failure of treatment.

**Record Keeping:**

All clinical information related to the study will be maintained as part of the medical record which is on a password protected hospital network.

**Efficacy Assessment**

While there are no studies comparing the efficacy of non-particulate dexamethasone to particulate steroids in the lumbar spine there is evidence in the literature showing efficacy for all steroids utilized in this study. The use of corticosteroids in TF ESI in the treatment of L–spine radicular pain has been advocated on the basis of several studies. In the only prospective randomized trial comparing triamcinolone to dexamethasone in cervical radicular pain, Dreyfuss showed no statistical difference at 4 weeks with both groups showing improvement.\(^{(18)}\) The triamcinolone group had 67% of the subjects with a >50% pain relief at 4 weeks compared to only 60% of the dexamethasone subjects having >50%
pain relief. This study showed a trend favoring triamcinolone but did not show a statistical significant difference due to a small sample size of 30. (18) There are no other prospective randomized controlled trials comparing non-particulate and particulate steroids in the treatment of spine radicular pain, and none in the lumbar spine.

There have been several other studies that demonstrate the efficacy of both betamethasone and triamcinolone in lumbar spine ESI. In a prospective study Ackerman showed that 25/30 subjects had complete or partial relief of pain with triamcinolone in lumbar spine ESI. (23) Stanczak completed a retrospective chart review of 597 subjects comparing the efficacy of triamcinolone (Kenalog) and betamethasone (Celestone) in treatment of lumbar radicular pain. The results favored Kenalog at 14 days with 75% of subjects showing improvement versus 54% of subjects that received Celestone. (19) A smaller retrospective chart review of 114 subjects comparing triamcinolone and betamethasone injection suspensions showed no statistical significant difference between betamethasone and triamcinolone, but the results showed a trend favoring triamcinolone (20)

There have been multiple studies that utilized triamcinolone, (24) (25) (26) (27) (28) and multiple studies have utilized Betamethasone (4) (29) (30) (31) (32) (33) for lumbar epidural steroid injections. While the studies each has individual flaws including: incomplete follow-up, non-standard outcome measures and lack of use of image guidance for the procedure; taken as a whole the body of literature supports an overall efficacy with approximately 50-60% of subjects achieving >50% pain relief after an ESI.

**Safety Assessment:**

Currently practitioners at the Rehabilitation Institute of Chicago are utilizing particulate steroids for all lumbar spine TF ESI. Subjects enrolled in this study will therefore have the same risk profile as those not enrolled in the study and completing the standard of care.

Overall the literature reveals that a lumbar spine TF ESI is a relatively safe procedure. There are several retrospective studies evaluating the side effect profile of lumbar spine TF ESI. Stalecup did a large retrospective cohort of 1,777 lumbar spine TF ESI over a 5 year period that showed an immediate post procedure complication rate of 5.5%. (34) All complications resolved without lasting sequelae. Approximately half of the subjects experienced transient leg weakness of light-headedness, and half had increased pain. The rates were higher for multi-level injections at 7.88% versus single level injections at 4.81%. In a retrospective study of a 24 hour post procedure questionnaire of 207 subjects that received a lumbar spine TF ES, Botwin found an overall complication rate of 9.6%. (35) The most common complications were non-positional headache at 3.1%, followed by increased back pain and facial flushing. The only prospective trial assessing the complication rate followed 217 subjects that had lumbar spine TF ESI, showed 91% of subjects having no complication or side effects. (36) Again all complications were temporary, and included: lightheadedness 2.8%, nausea 1.4%, increased radicular pain 0.9%, non-specific headache 0.5%, and vasovagal reaction 0.5%. A soon to be submitted
for publication retrospective study of 2563 injections at the Rehabilitation Institute of Chicago, showed a complication rate of 9.2% for ESI. The most common complications included vasovagal reactions at 4.1% followed by increased pain at 0.7%.

The major complication of paraplegia has only been reported seven times in the literature. Several steps have been taken in the design of this study will nullify this potential risk, even for subjects receiving the particulate steroid. Since the radicular artery has been shown to in cadaveric dissections to have variability as far caudal as the L2 spinal level, subjects will only be randomized if their target pathology below the L3 level. This should effectively eliminate the risk of inadvertent arterial injection. This step alone should effectively eliminate the potential risk of paraplegia associated with particulate steroids.

In addition to this several other steps will also taken to avoid any potential complications from this procedure. The procedure will be conducted under sterile conditions to minimize any chance of infection. Fluoroscopy will be utilized to determine appropriate needle placement and observe real-time dye flow after a test injection of contrast medium. Several of the case reports utilized computer tomography (CT) guidance to guide needle placement, combined with needle aspiration. However, aspiration lacks sensitivity for detecting intravascular placement. Intravascular injection (confirmed with contrast dye) in the setting of a negative aspiration has been reported in 11.2% of 761 consecutive transforaminal ESIs. Furman found only a 44.7% sensitivity of a positive flash or aspiration with lumbosacral transforaminal injections utilizing a 22-gauge spinal needle. Fluoroscopy has the added benefit over CT of being able to observe real-time contrast medium flow. Even with appropriate placement of the needle using anatomic landmarks, inadvertent intra-arterial injection can occur. This combined with the low sensitivity of aspiration for arterial injection necessitates the use of a test injection of contrast medium with real time fluoroscopy.

As evidenced by the case reports of paraplegia post lumbar spine TF ESI that utilized real time fluoroscopy, angiography alone is sometimes not sufficient for detecting intra-arterial injection as the angiogram can be fleeting. Therefore a test injection of local anesthetic prior to the injection of corticosteroids will be utilized with all subjects. Karasek and Bogduk presented a case of transient paralysis after a test injection of local anesthetic prior to a planned cervical TF ESI. The procedure was terminated, and the patient suffered no permanent impairments. This occurred in the presence of a negative angiogram, and reinforces the merit of injection a local anesthetic separately and prior to the injection of any corticosteroid. By utilizing a test injection the operator can evaluate if the injectate has reached the spinal cord. This step also serves to make the injection less painful.

There has not been a case report of a spinal cord injury when utilizing the steps outlined above. Therefore, when consistently preformed, the above steps can help reduce potential serious complications regardless of steroid utilized.

Since patients scheduled to undergo lumbar spine TF ESI are currently receiving particulate steroids, subjects randomized in this study to receive non-particulate
(dexamethasone) may actually have a better safety profile. Regardless an interim analysis will be preformed to assess safety, efficacy, and need for more/less subjects.

**Statistical Analysis:**

Statistical analysis was preformed to determine whether there is a difference in pain after an injection to detect observed differences in rates of response to treatment with 80% power and a P value of .05. A thorough review of the literature demonstrates a variable therapeutic effect of ESI, with most showing an approximately a 50-60% therapeutic effect in pain at 2-4 weeks post epidural steroid injection.

Utilizing dichotomous outcomes to show differences of 60% and 30% will require 48 patients in each group. To differentiate even smaller differences of 55% success versus 45% success would require close to 400 patients in each group. Target of 60 patients in each arm to allow for anticipated attrition rate of 20%.

An interim analysis will be conducted when 60 subjects have been enrolled and completed follow-up. Adjustments in total number of subjects needed may be made based upon these results.

**6. ANTICIPATED RESULTS AND POTENTIAL PITFALLS**

Based on a thorough review of the limited available literature, it is suspected approximately 50-75% of all subjects, regardless of steroid received will show clinically meaningful improvements in pain. It is also suspected that subjects receiving particulate based triamcinolone could show a trend towards increased efficacy when compared to dexamethasone, but without reaching statistical significance.

This study is not a safety assessment of the various steroid compounds, but rather looking for major differences in efficacy associated with the various steroid compounds. Therefore while any potential complication will be recorded and reported, it is not anticipated within any arm of this study. The study was designed to minimize any potential risk to the subjects; regardless a planned interim analysis will assess efficacy and safety after 50% of the subjects have been enrolled and completed the anticipated follow-up.

There are several potential downfalls that could occur during this study. First is subject recruitment, due to the requirement of extra follow-up and paperwork associated with the study outcome measures. Therefore an incentive of $50 for the first office visit, $100 for the second visit at 3 months, and $150 for the 6 month office visit (to a maximum of $300) will be given to subjects to reimburse them for travel, time, and parking associated with the required follow-up.
Another potential downfall with this study is that co-interventions will not be standardized. Based on standard practices at the Rehabilitation Institute of Chicago most subjects will receive physical therapy in addition to the injection. For logistic reasons the use of pain medications will not be standardized or restricted. This may add a confounding variable when assessing pain relief at follow-up. The utilization and prescription of all types of pain medications (anti-inflammatory, opioid, non-opioid, neuropathic, etc) will be documented, tracked, and analyzed for statistical difference. Also subjects will be limited to those with obvious one level, unilateral pathology correlated on history, physical exam, and imaging. Those with multiple pain generators will also be excluded from the study in order to help decrease the need for additional different interventional treatments.

Another problem with this study will be the overall lack of power. Even though the risk of paraplegia is very small with any Lumbar spine TF ESI, the potential complication is significant and life altering especially for a voluntary procedure. Therefore this study was not designed to differentiate small differences in efficacy between steroids, but rather to determine if major deficiencies when comparing aqueous non-particulate dexamethasone to particulate triamcinolone or betamethasone. To differentiate small differences in efficacy will require large numbers of subjects or multiple studies.

7. DISCUSSION OF NEXT STEPS

The results of this type of study are eagerly anticipated in the interventional spine community. This study will allow practitioners to have more information, which will allow for informed risk and benefit discussions of various steroid compounds with their patients. Depending on the overall efficacy of the various steroids, physicians may even choose to change their first line medication choice for patients needing a high lumbar TF ESI in order to reduce the risk of paraplegia.

As noted above, this study is not designed to determine small differences in efficacy between the various steroid compounds. Therefore possible future studies could include repeating and validating similar findings by other physicians or completing a larger study with increased power to differentiate small differences in efficacy, especially between the two particulate steroids available.

Also for pragmatic reasons this study was limited to single level spinal pathology. Patients with multilevel pathology or degenerative spinal stenosis are excluded from this study. A comparison of steroid efficacy with this different disease pathology would be indicated as a next step.

Works Cited


