Title: Intradiscal Platelet-Rich Plasma Injection for Chronic Discogenic Low Back Pain

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Objectives:
To assess changes in pain, physical function, health-related quality of life and cost-effectiveness in patients with discogenic low back pain after an intradiscal injection of PRP.

Introduction

Low back pain is one of a few conditions which affects all individuals through the lifespan. The etiology of low back pain is multifactorial and in many cases self-limiting, however it also is the leading cause for working age adults to be disabled with more than $87 billion spent on low back pain disorders in 2013[1] Lumbar disc herniation and internal disc disruption are two causes more common in these younger age groups [2]reaching 39-42% with a predicted probability above 60% until age 50y. While the natural history of disc herniation suggests most individuals will return to a prior level of function in 3-6 months, there is a high rate of recurrent episodes which can cause short-term disability. Continued pain from a discogenic source can lead to decreased activity levels and accelerate degenerative changes in the disc and facet joints as described by Kirkaldy-Willis.

Current guidelines for treatment of axial low back pain from discogenic sources including those with radiculopathy include a 6-12-week course of conservative care including medications, therapy, acupuncture, chiropractic and exercise before an interventional paradigm of injections and/or surgical treatment. For those individuals who do not improve with conservative care and have predominately axial pain, options are limited as success rates from epidural steroid injections and surgery are 50% or less. Other treatments include chymopapain injection, intradiscal electrothermal annuloplasty (IDET), nucleoplasty, methylene blue injection[3,4], ozone injection[5] , fibrin sealant injections[6]. All of which have 50% or less likelihood of reducing pain more than 50%, although much of this data is from uncontrolled or prospective case-control studies only.

Platelet- rich plasma (PRP) injections stand apart from those listed above in that they are purported to be “regenerative” interventions for the diseased lumbar disc. PRP is a concentrated injectant of growth factors and anabolic factors which have in vitro and animal studies that have demonstrated upregulated proteoglycan synthesis and nucleus pulposus proliferation, restoration of disc height, healing of annular puncture wounds and anti-inflammatory effect with down regulation of TNF-alpha and IL-1.[7] There has been limited clinical trials in humans on the effect of intradiscal PRP, including 3 trials of which 1 is a RCT and 2 are prospective series. Efficacy of intra-discal injection has shown statistically significant benefits in reduction in pain, improvement in physical function at follow-up points from 3-24 months. Each of these trials have limited sample sizes, short duration follow-up and lack of a standardized PRP preparation, making the generalizability difficult.

Subjects
A total of 100 subjects, aged >18 years old on the day of enrollment, will be recruited for participation in this study.
De-identification
All subjects will be assigned a unique alphanumeric identifier. No personally identifiable information will be used in the final database. All data will be stored on a highly secure, password protected computer.

Participant Recruitment

Our intended subject demographic includes an active population between the ages of 18 and 80 years on the day of enrollment. We intend to recruit participants primarily through word-of-mouth. Additionally, recruiting will take place through the distribution of flyers to the Health Sciences Education Building, University of Utah Student Life Center, the University of Utah Orthopaedic Center, and the University of Utah hospital. Upon first contact with the potential participant, the study coordinator or research associate will provide a basic description of the study and review inclusion and exclusion criteria and discuss general health status. Interested volunteers who qualify will be asked to report to the University of Utah Orthopaedic Center. Prior to screening procedures and after being informed of any potential risks involved in the study, volunteers will be asked to provide written, informed consent for study participation.

Inclusion Criteria:

1) Age greater than 18 years of age at day of enrollment.
2) Clinical diagnosis of refractory discogenic low back pain for >3 months.
3) Magnetic resonance imaging pathology consistent with clinical symptoms/signs or positive lumbar provocative discography according to SIS/IASP standards at one or two levels.
4) Back pain greater than leg pain with an intensity of at least 4/10 or higher using the Numerical Rating Scale (NRS).
5) Pain duration of more than 12 weeks despite trial of conservative therapy (medications, physical therapy, or chiropractic care) for 2 months.

Exclusion criteria:

1) Refusal to participate, provide consent, or provide follow-up information for the 24-month duration of the study.
2) Contraindications to intradiscal injection of PRP (active infection, bleeding disorders, current anticoagulant or antiplatelet medication use, allergy to iodinated contrast, penicillin or clindamycin and pregnancy or breastfeeding).
3) More than 2 levels of clinical or discogram proven pain.
4) Non-discogenic source of low back pain as identified by separate diagnostic blocks.
5) Negative lumbar provocation discography.
6) Active moderate to severe lumbar radiculopathy.
7) Intradural disc herniation.
8) Spinal fracture within the past 6 months.
9) Steroid injection in the spine within the last 30 days.
10) Any intradiscal injection other than contrast dye or anesthetic in the last 30 days.
11) Prior fusion at level considered to be the source of the pain.
12) Prior lumbar spine surgery within the last 6 months.
13) AP diameter of spinal canal less than or equal to 9mm at level to be treated.
14) Severe uncontrolled medical condition.
15) Moderate to severe hepatic dysfunction.
16) Severe psychological illness.
17) History of Inflammatory arthritis.
18) Malignancy within past 5 years except basal cell or squamous cell skin cancer.
19) Current use of equal to greater than 30mg morphine-equivalent per day of opioid use.
20) A history of alcohol or drug abuse within past 5 years.

21) Use of any investigational drug within past 30 days.
22) A known allergy or sensitivity to citrate (used for processing PRP).
23) Severe anaphylactic/anaphylactoid reaction to any medications used.
24) Pending litigation involving subject's back pain.
25) No insurance coverage for any subsequent tests or procedures.
26) Disc protrusion greater than 5mm from base of vertebral body.
27) Greater than 50% disc height loss at involved level(s).
28) Inability or unwillingness to continue rehabilitation protocols.

Study design:
Survey/Questionnaire research
Observational research
Prospective Clinical Research

Power Analysis
Size of study groups: 100 total participants.

Procedures:
All visits are standard of care, however completion of questionnaires will be for study purposes in follow-up clinic visits and at specified time-frames. Study involvement includes the following visits:

Screening: Questionnaires and clinical examination
Enrollment: Questionnaire and clinical examination
Follow-up:
1 month post-injection- questionnaires and clinical exam
2 months post-injection- questionnaire and clinical exam
3 months post-injection- questionnaire and clinical exam
6 months post-injection- questionnaire and clinical exam
9 months post-injection- questionnaire and clinical exam
12 months post-injection- questionnaire and clinical exam
24 months post-injection- questionnaire and clinical exam
36 months post-injection- questionnaire and clinical exam

Questionnaires: Demographics, medication use (MSQ III), ODI, PROMIS PF CAT, PROMIS Global 10, NRS for back and leg pain (current, average last week), PGIC score, PSQ-3, and patient satisfaction with treatment score (5 point: 1, very dissatisfied; 2, dissatisfied; 3, neither satisfied nor dissatisfied; 4, satisfied; and 5, very satisfied).

Data Collection:

An electronic data collection sheet (via iPad) will be used to record all pre-procedure data (see data collection sheet):

1) Age (years).
2) Sex.
3) Height (cm).
4) Weight (Kg).
5) Duration of pain (weeks).

6) Radiologic diagnosis based on MRI of the Lumbar Spine.
7) NRS for pain; separate scores for back pain and for leg pain

8) Oswestry Disability Index (ODI)
9) PROMIS Physical Function scale version 2
10) PROMIS Global 10
11) Medication Quantification Scale (MQS III) score
12) Daily opioid use in morphine equivalents

Additional questions for post procedure survey

13) Patient Global Impression of Change (PGIC)
14) Patient satisfaction score (five-point Likert scale: 1, very dissatisfied; 2, dissatisfied; 3, neither satisfied nor dissatisfied; 4, satisfied; and 5, very satisfied)

Immediately after injection the following will be obtained:

15) Fluoroscopy time
16) Post-injection NRS pain score; separate scores for back pain and for leg pain
17) Adverse events, if they occurred

Data Storage:

Hard copy data will be collected and stored in a password-protected computer located in the Division of PM&R. Participants will each be assigned an ID number that will be used as the sole identifier on any documents. Participant data will be compiled onto a single password protected file, where they will only be identified by their ID number. An enrollment log will be the only file where subject names are correlated with ID numbers. This will be kept in a separate, secure, password-protected file in the Division of PM&R.

Data Analysis Plan

The primary outcome will be the proportion of participants with >80% and >50% reduction in back pain on the NRS pain score at the 2-month follow-up assessment. Secondary outcomes included reduction in median NRS pain score, ODI, change in PROMIS PF-CAT, MQS III, opioid consumption in daily morphine equivalents, PGIC score, PSQ-3, and satisfaction score. Secondary outcomes will also be defined based on categorical “responder analysis” definitions of important clinical change given the National Institutes of Health recommendation for responder analysis in the assessment of therapeutic spine pain interventions. The responder analysis will include the proportion of patients with 30% or greater improvement on the ODI, a PGIC score less than 3 (indicating “improved” or “very much improved”), a 6.8 or greater point reduction on the MQS III score (equivalent to approximately 10 daily morphine equivalents), and the proportion of participants who undergo surgical spine surgery in the study period.

Statistical analysis

Means and standard deviations of subject demographic data, as well as pain, functional, and treatment satisfaction scores will be calculated. Intergroup differences will be assessed by t test for numerical data and Chi Square or Fisher Exact test for categorical data. Regression modeling will be implemented using ANOVA to assess for patient traits and characteristics that increase the likelihood of efficacy using one technique as opposed to the other.

Risks/Benefits:

Risks of study participation are the same as those for any standard fluoroscopically guided lumbar intradiscal injection performed in the PM&R Spine Clinic. These include: local infection, intradiscal infection (discitis), epidural hematoma or abscess, dural puncture and potential post-dural puncture headache, paresthesia during needle placement, pain at the injection site, failure to relieve pain, allergic reaction to products or medications being used. Utilizing fluoroscopy, the risk of nerve damage, spinal cord injury or intravascular injection is less than 1:500,000. The length of stay and length of recovery is no longer than that of a standard spinal injection performed in the PM&R Spine Clinic at present.

There are no direct benefits to the individual by participating in this study. The patients will be presented with the same options of treatment whether they enroll in the study or decide not to. The information extracted from this study may provide the investigators a better understanding of a patient's short and long-term pain response and physical function following a intradiscal PRP injection.

Study Termination Criteria

- Adverse events considered/identified by the medical staff during the procedure process
- The subject requests to be withdrawn from the study during the procedure.

Safety Monitoring Plan

Safety will be monitored by all members of the study team:

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The Principal Investigator is a physician at the University of Utah Health Sciences Center. Members of the data and safety monitoring committee will be in close contact with all the subjects throughout the study, both in-person and via telephone. The members of the data and safety monitoring committee will review potential side effects and adverse reactions with each subject at the time of delivery of the study drug and at the time of each sample collection. All the committee members are located at the University of Utah Orthopaedic Center; all members have research experience.

References

1. Dieleman JL, Baral R, Birger M, et al. US Spending on Personal Health Care and Public Health, 1996-2013. *JAMA.* 2016;316(24):2627-2646.

2. DePalma MJ, Ketchum JM, Saullo T. What is the source of chronic low back pain and does age play a role? *Pain Med.* 2011;12(2):224-233.

3. Guo X, Ding W, Liu L, Yang S. Intradiscal Methylene Blue Injection for Discogenic Low Back Pain: A Meta-Analysis. *Pain Pract.* 2018.

4. Levi DS, Horn S, Walko E. Intradiskal methylene blue treatment for diskogenic low back pain. *PM R.* 2014;6(11):1030-1037.

5. Hashemi M, Poorfarokh M, Mohajerani SA, et al. Injection of intradiscal o2-o3 to reduce pain and disability of patients with low back pain due to prolapsed lumbar disk. *Anesth Pain Med.* 2014;4(5):e19206.

6. Yin W, Pauza K, Olan WJ, Doerzbacher JF, Thorne KJ. Intradiscal injection of fibrin sealant for the treatment of symptomatic lumbar internal disc disruption: results of a prospective multicenter pilot study with 24-month follow-up. *Pain Med.* 2014;15(1):16-31.

7. McGuire RA, Chen Z, Donahoe K. Dual fibular allograft dowel technique for sacroiliac joint arthrodesis. Evid-Based Spine-Care J. 3 (3): 21–28. Buchowski JM, Kebaish KM, Sinkov V, Cohen DB, Sieber AN, Kostuik JP (2005) Functional and radiographic outcome of sacroiliac arthrodesis for the disorders of the sacroiliac joint. Spine J Off J North Am Spine Soc. 2012;5(5):520–8.