Discogenic Low Back Pain: Stem Cells Solution?

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Disclosures

• none
Objectives

- Discogenic pain - pathophysiology, diagnosis and incidence
- Treatment options for discogenic pain
- Latest in stem cells for discogenic pain
- New APM/MAPS study
LBP: Sitting Intolerance

- 52 yr old female, increased back pain upon sitting; straining in the bathroom
- Prior diagnostic workup- negative for SI joint and facet joint pain.
- Unresponsive to physical therapy and medications.
- Diagnostic evaluation:
  - Neurosurgeon referred her for discogram
    - Is this appropriate?
    - Therapeutic options
    - If positive and she has surgery, what is the cost and what is the success
    - If she “fails surgery” then what?
Posterior Element of Pain Increases as we Age

Thigh Pain Absent

Predicted Probability

Age (years)

SJP
FJP
IDD
Patient’s history has lots of clues
Pathology of Internal Disc Disruption

- Large Vertical Forces
- Repetitive Torsion Loads

  - End Plate Disruption
    - Inflammation or autoimmune response
    - Degradation of disc
      - Chemical and mechanical nociception
        - Discogenic Pain
Innervation of the painful disc

- The outer annulus is densely innervated
- The disrupted portions of the disc becomes infiltrated with neurovascular bundles
- Inflammatory mediators heighten nociception and sensitize the nerve endings
Mechanisms

- Disc degeneration and injury-centripetal growth of nerve fibers in the disc
- More extensive disc innervation in the severely degenerated human lumbar disc compared with normal discs
- Small unmyelinated nerve components, extensive innervation of the inner parts of the annulus
- The nociceptive properties-substance P immunoreactivity

Coppes MH. Spine 1997;22:2342-2349
Pathology
Disc Changes

- Vascular ingrowth observed in peripheral tears of the annulus (Hirsch 1953)
- Nociceptors accompany vascular growth—presence of sensory nerve supply in the inner annulus.
- In DDD an association between in growth of nerves expressing substance P and disc degeneration. The extent of neoneuralization greatest at the painful levels. (Freemont et al 1997)

Endplate Changes

• Degenerative changes-increased vascularization of the endplates.

• Nerve elements around endplate vessels, role in pressure related pain sensation.

• Correlated the extent of memory pain as determined by discography with the amount of vascularization in the endplates on histological examination.

• The extent of vascularization in the degenerated endplates - moderate correlation with VAS scores after discography.

Weisskopf M. Zeitschrift fur Orthopadie und Ihre Grenzgebiete. 142:174-8, 2004
Pain in IDD relative to imaging

• Source of pain is not readily evident on imaging but CT/discography provides physiologic approximation

• Schwarzer AC et al. The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. Spine 20:1878-1883,1995
Normal MRI but tear in outer annulus
Could the tear cause pain? YES!
Need to understand the basic innervation
Analysis of suspected of discogenic pain

- MRI disc degeneration predicts LBP, if...HIZ (high intensity zone) present.
- HIZ on MRI correlated 65-95% of the time with pain-producing fissured disc

### MRI Results: “Normal” Subjects (N = 67)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Under 60</th>
<th>Over 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herniated disc</td>
<td>22%</td>
<td>36%</td>
</tr>
<tr>
<td>Spinal Stenosis</td>
<td>1%</td>
<td>21%</td>
</tr>
<tr>
<td>Bulging disc</td>
<td>54%</td>
<td>79%</td>
</tr>
<tr>
<td>Degenerated disc</td>
<td>46%</td>
<td>93%</td>
</tr>
</tbody>
</table>
Imaging Hazards

“A diagnosis based on MRI, in the absence of objective clinical findings, may not be the cause of a patient’s pain, and an attempt at operative correction could be the first step toward disaster.”

Boden et al., JBJS, 1990
Determinants of Lumbar Disc Degeneration

- Disc degeneration may be explained primarily by genetic influences and complex unpredictable interactions of unidentified factors.

Environmental factors affect homeostatic mechanisms

FGF = fibroblast growth factor; BDGF = brain-derived growth factor; NGF = nerve growth factor; NO = nitric oxide. TIMP = tissue inhibitor of matrix metalloproteinases

Twin Studies (Gene Therapy)

- 52-74% Heritability of DD as seen in twin studies
- Genetic factors become more evident at older age
DISC STIMULATION

Disc stimulation

Negative
Prevent surgery

Positive
Surgery
Therapeutic Interventions for IDD

Lumbar instrumented fusion: No better than intensive rehabilitation


Lumbar disc arthroplasty: non-inferior to instrumented fusion

Treatments: Tried and Failed

Intradiscal Injections:
- Steroids
- Indigo Carmine/Methylene Blue
- Antibiotics

Heating Procedures
- RFA
- IDET
- Disctrode
- Nucleoplasty
Intradiscal Steroids

• Studied response to intradiscal injection of corticosteroids in chronic low back pain

• At 3 and 6 months, IDIC tended to be more effective in the Modic I and Modic I-2 groups but not significantly. No complications such as infection or hematoma were reported. IDIC could be a short-term efficient treatment for patients with chronic LBP and predominantly inflammatory endplate changes when conservative treatments have failed.

Intradiscal Antibiotics

• Injected in HNP and Modic Type I changes
• Chronic LBP with or without Sciatica
• Amoxicillin/Clavulanate 500/125mg tid 100 days
• Pain relief gradual 6-8 weeks
• Double Dose More Effective but NS
• Relief endured beyond Rx

Propionibacterium acne & Corynebactarium propinquum
Intradiscal Heating Procedures

**RF Cannula**
Intradiscal RF
Sluijter, 1994

**SpineCath®**
IDET
Smith and Nephew, 1998

**discTRODE™**
RF Annuloplasty
Tyco / Radionics, 2000
Biacuplasty

- Radiofrequency current is concentrated between electrodes on two straight probes.
- The electrodes are internally cooled allowing deep, even heating and eliminating tissue adherence.
- Temperature sensors allow monitoring at the electrode tips and disc periphery.
- The ideal temperature profile is 55-60°C in the inner posterior disc decreasing to 45°C in the peripheral edge of the posterior disc.
Treatments: Currently Considered

Soups and Cocktails
  PRP
  Fibrin Glue

Biologics
  Growth Factors
  Gene Therapy
  Cell therapy
  Tissue Engineering

HF10 SCS Therapy
HF10 SCS Therapy
Biologic Treatments For Discogenic LBP

• Protein Factors
• Gene Transfer
• Cell Therapy
• Tissue Engineering
Biomolecular Treatments

• Two categories:
  – Recombinant Proteins: alters the biosynthesis at protein level
  – Gene Therapy: alters the biosynthesis at gene level

• Sufficient Viable Cells Must Be Present
• Rapid diffusion & degradation a problem
• Thus suitable for EARLY stages DD
Biological Treatments: Direct Injection of GH, Anabolic Enzymes

Active substance (growth factor, enzyme, etc.) → Injection into degenerated disc → Active substance embedded in slow-release matrix
Biomolecular Treatments: Recombinant Proteins

• GF stimulate disc cells resulting in ECM Synth
  – TGF beta
  – GDF
  – BMP 7
  – PDGF
  – IGF 1
  – Link N (Link protein)

• Incidentally, Simvastatin effect is mediated via BMP 7
Intra-discal Simvastatin

- Effect mediated through BMP (bone morphogenetic proteins)
- Induces chondrogenesis
- Induces production Type II Collagen and Aggrekan
Gene Therapy: Balancing Act

• Knocking off the Genes that are involved in DDD. e.g. si-RNA (Interfering RNA)-Silences the proteins is involved in degeneration of IVD

• Enhance genes which are involved in regeneration or growth factors e.g. TGF, IGF, PDGF
Gene transfer to degenerated disc via recombinant viral vector promoting endogenous synthesis of therapeutic protein.
Disc derived Stem Cells (Cell Therapy)
Bone Marrow Derived Stem cell

- Harvesting of autologous progenitor cells
- Ex vivo cell expansion
- Differentiation
- Intervertebral disc-like cells
- Injection of MSCs or differentiated cells into degenerated intervertebral disc
Goals of interventional treatment (pain relief, improved disc microenvironment, and tissue regeneration).

Models for mesenchymal stem cell (MSC) concentration and/or isolation prior to fluoroscopically-guided intradiscal injection.

Meta Analysis: Stem Cells
Oehme et al.

• Important considerations when assessing stem cell study results in animal models of lumbar disc degeneration:
  • Persistence of notochordal cells
    • May demonstrate native regenerative effects
  • Physical differences
    • Quadruped posture → differences in shape, composition and biomechanics
    • Small disc dimensions in smaller animal models
      • Disproportionate volumes and distances compared to humans
  • Method of degeneration induction used
    • Chemical vs. mechanical nucleotomy may impact degenerative cascade
• Disc Chondrocyte Transplantation
  • Use of NP Cells isolated from intervertebral disc tissue, culture expanded
    • Favorable outcomes in 12 of 14 basic science studies, and 1 clinical
      • Improved morphological and histological, Increased proteoglycan content, Disc height preservation
      • Human clinical- improved clinical outcomes at 2 years
  • Issues with isolating, expanding and storing prohibitive
  • Allogenic NP cells still under investigation as option
Meta Analysis: Stem Cells
Oehme et al.

- **Transplantation of MSCs, MPCs, and other Stem Cells**
  - MSCs can be isolated from various tissues, nonimmunogenic, non-malignant transformation
  - Self-renewing
  - Evidence that shows repair of damaged discs, at least partially
  - Allogenic cells taken from young healthy donor and utilized as “off the shelf” product
  - Questions remain:
    - What is ideal cell dose?
    - What is ideal carrier for administration?
    - Longevity and lifespan of cells within disc?
    - Survival of MSCs ranged from 2 to 24 weeks vs. Transplanted NP cells from 8 weeks to 8 months
      - Leakage out of injection site issue
  - **Mechanism of Action of Transplanted Cells**
    1. Cells survive and proliferate in target disc, acting as chondrocyte-like disc cells → Produce proteoglycan and collagen extracellular components
    2. Paracrine effect → release tropic factors that stimulate resident cells to produce matrix
    3. Pain reduction → potential by product of the factors produced by transplanted cells such as TNF-alpha
Mesoblast- Phase 3

A Prospective, Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of rexlemestrocel-L alone or Combined with Hyaluronic Acid (HA) in Subjects with Chronic Discogenic Lumbar Back Pain through 36 Months
Indication

• Treatment of chronic discogenic lumbar back pain (> 6 months duration) associated with moderate degenerative disc disease (DDD)
Purpose

- To determine Overall Treatment Success of rexlemestrocel-L alone or rexlemestrocel-L+HA at 12 and 24 months based on a composite responder analysis of low back pain Visual Analogue Scale (VAS) score, Oswestry Disability Index (ODI) score and no post-treatment interventions affecting the treated disc.
Follow-ups

• Subjects will be followed for approximately 36 months post treatment and evaluated at baseline, treatment day (Day 0), 1, 3, 6, 12, 24, and 36 months post-treatment

• The primary endpoint for evaluation of safety and effectiveness will be conducted at 24 months. Longer-term safety and effectiveness assessments will be conducted at 36 months.
Design

• Prospective
• Multicenter
• Double Blind
• Placebo (defined as saline) controlled
• Randomization, by study site, with the randomization ratio of 1:1:1 between
  a. Treatment Arm 1: 6 million rexlemestrocel-L cells
  b. Treatment Arm 2: 6 million rexlemestrocel-L cells + HA
  c. Treatment Arm 3: saline
Design

- Screening Period: Day -75 to Day 0
- Randomization: >= 7 days prior to Day 0
- Visit 1: (Screening)
- Visit 2: (Injection - Day 0)
- Visit 3: (1 month)
- Visit 4: (3 months)
- Visit 5: (6 months)
- Visit 6: (12 months)
- Visit 7: (18 months)
- Visit 8: (24 months)
- Visit 9: (36 months)
- Visit 10: (Long-term Safety Follow-up)

Groups:
- Rexlemestrocel-L alone (120 subjects)
- Rexlemestrocel-L + hyaluronic acid (120 subjects)
- Saline control (120 subjects)
Key Study Criteria:

- Are 18 years of age or older and considered skeletally mature (we would prefer patients between the ages of 18 and 40)
- Have been diagnosed with moderate degenerative disc disease from L1 to S1, with **ONE** symptomatic level
- Have had chronic back pain for at least 6 months
- Have failed conservative treatment which includes NSAIDs, Opioids, Acupuncture, pool therapy and the like, for at least 3 months
- Have undergone supervised physical therapy for the treatment of low back pain.
- Have had no lumbar back surgery
Trial Results: MPC-06-ID
Phase 2 Chronic Low Back Pain Due to Disc Degeneration Clinical Trial

• *Improvement in chronic low back pain.* At both 6 and 12 months, a reduction in pain from baseline of 50% or more, without any additional intervention, was seen in 59.3% of the MPC-06-ID group, 44.8% of the 18 million MPC group, 18.8% of the saline group, and 15.8% of the HA group, as measured by visual analog scale, or VAS (p = 0.006 across all four groups, p=0.023 for 6 million MPC against saline and p=0.006 against HA).
Trial Results: MPC-06-ID
Phase 2 Chronic Low Back Pain Due to Disc Degeneration Clinical Trial

MPC groups have a greater proportion of patients with at least a 50% improvement in back pain at both 6 and 12 months relative to controls.

% patients with 50% VAS reduction from baseline and no intervention

% patients with improvement in pain at both 12 & 24 months

- Saline: 12.5%
- HA: 22.2%
- 6M MPC: 48.2%
- 18M MPC: 33.3%

Advanced Pain Management
we know your pain

MAPS Applied Research Center
Trial Results: MPC-06-ID
Phase 2 Chronic Low Back Pain Due to Disc Degeneration Clinical Trial

• *Improvement in function:* At both 6 and 12 months, an improvement in function from baseline of 15 points or more, as measured by Oswestry Disability Index, or ODI, without any additional intervention, was seen in 50.0% of the MPC-06-ID group. 48.3% of the 18 million MPC group, 31.6% of the HA group, and 17.7% of the saline group (p=0.05 MPC-06-ID versus saline, p=0.06 18 million MPC versus saline).
Trial Results: MPC-06-ID
Phase 2 Chronic Low Back Pain Due to Disc Degeneration Clinical Trial

MPC groups have a greater proportion of patients with at least a 15 point improvement in function from baseline as measured by ODI at both 6 and 12 months, relative to controls.