Transdiscal Biacuplasty

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Disclosure

• Relevant to this presentation:
  PI in Kimberly Clark sponsored RCT (completed)
  Dr. Kapural provided some slides and data
• Other disclosures:
  President of World Academy of Pain Medicine Ultrasonography (www.wapmu.org)
Content:

- Discogenic pain: does it exist?
- Minimally invasive treatments
- Intradiscal “stuff”
- Biacuplasty
DEGENERATION AND AGING
Disc Pathophysiology

- Disc degeneration and injury cause centripetal growth of nerve fibers into the disc. There is extensive disc innervation in the severely degenerated human lumbar discs compared to normal discs.

- Small unmyelinated nerve components, extensive innervation of the inner parts of the annulus.

- Nociceptive properties—substance P immunoreactivity.

- Vascular in-growth observed in peripheral tears of the annulus.

- Small, post-traumatic peripheral tears of the annulus fibrosus lead to an acceleration in dehydration of the intervertebral disc.

Possible Scenario

Loss of Nuclear Hydrostatic Pressure

- Delamination
- Fissuring
- Microfracutures of collagen fibrils

Sensitization of Nonciceptors

- PLA2, NO, IL1
- Repetitive stimulation of DRG

Saal and Saal, 2002; Ozaktay et al., 1998; Schwartzet al., 1995
Infection?

- Of the 61 patients undergoing surgery for extruded disc herniation in their series, in 46% of specimens growth of Propionibacterium Acnes [PA] was observed, and this correlated with a greater frequency of MC type I


- RCT involved 162 patients were randomized to receive either 100 days of treatment with Bioclavid (Amoxicillin/Clavulanic acid) vs. placebo. At one year the authors concluded “(patients) who were treated with antibiotics obtained statistically significant improvements compared to the placebo group in all measured parameters”

“DISC DEGENERATION MAY BE EXPLAINED PRIMARILY BY GENETIC INFLUENCES AND COMPLEX UNPREDICTABLE INTERACTIONS OF UNIDENTIFIED FACTORS.”

Extra-Discal Minimally Invasive Methods

• Epidural steroids: ineffective
• Transforaminal injections: + short-term results
• Rami communicans RF: + intermediate-term results, limited evidence


• L2 DRG pRF – (44.44%) of 45 patients had pain relief >or= 50% at 1 year follow up

Therapeutic Disc Injections
Methylene Blue

RCT (n 72) showed extraordinary results: at the 24-month follow-up the patients in MB injection group showed a mean reduction in NRS of 52.50, a mean reduction in Oswestry disability scores of 35.58, and satisfaction rates of 91.6%, compared with 0.70%, 1.68%, and 14.3%, respectively, in placebo treatment group (p<0.001, p<0.001, and p<0.001, respectively). No adverse effects or complications were found in the group of patients treated with intradiscal MB injection.

Methylene Blue?

“Peng et al. announced astounding results, unprecedented and unrivalled in the history of research into the treatment of chronic discogenic low back pain. For these outcomes the NNT was 2. Against these figures, the results of surgery, rehabilitation, behavioural therapy, and any other treatment for back pain pale into insignificance.”

Intradiscal Steroids

• RCT (n 120): + short-term benefit

• RCT (n 120): no effect
Other Agents

- Intradiscal Glucosamine Chondroitin Sulfate
- Intradiscal Etanercept
- Intradiscal Simvastatin
- Intradiscal Injectable Synthetic Nucleus
- Intradiscal Fibrin Sealant
- Intradiscal BMP-2
- Intradiscal OP-1 (BMP-7)
- Intradiscal GDF-5
- Intradiscal Stem cells
Investigational Biologic Approaches

• Metabolic agents - Proteins and drugs to metabolically enhance extracellular matrix
• Cells - Cellular supplementation to increase extracellular matrix synthesis
• Tissue scaffolds - Conductive scaffolds to cellular migration, proliferation and extracellular matrix synthesis in three dimensions
• Cytokine inhibitors – reduce inflammation
Intradiscal BIOSTAT BIOLOGX Fibrin Sealant

- **BIOSTAT BIOLOGX**
  - Purified human fibrinogen and thrombin, calcium chloride, and aprotinin acetate (synthetic)
  - Rapid catalytic conversion of fibrinogen into a dense three dimensional fibrin scaffold
- Flows into and seals annular defects
- Functions as a resorbable conductive tissue scaffold
- Reduces the metabolic synthesis of inflammatory cytokines and proteolytic enzymes
Pilot Study Design

• Prospective multi-center non-randomized FDA pilot study investigating safety and efficacy of the Biostat System in patients with symptomatic IDD

• 15 patients at 3 centers (5 patients each)

• Single level or two contiguous levels of disc pain

• 26 weeks primary endpoint with extended follow-up at 52 and 104 weeks
### VAS Low Back Pain

(thanks to Dr Aaron Calodney)

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>AVG Individual Change from Baseline</th>
<th>AVG % Individual Change from Baseline</th>
<th>≥ 30% Improvement (% of Patients)</th>
<th>≥ 50% Improvement (% of Patients)</th>
<th>≥ 75% Improvement (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 hr</td>
<td>-28.5 mm</td>
<td>-36.9%</td>
<td>57.1%</td>
<td>40.0%</td>
<td>20.0%</td>
</tr>
<tr>
<td>1-week</td>
<td>-37.0 mm</td>
<td>-45.2%</td>
<td>64.3%</td>
<td>46.6%</td>
<td>33.3%</td>
</tr>
<tr>
<td>4-week</td>
<td>-41.8 mm</td>
<td>-52.9%</td>
<td>73.3%</td>
<td>66.7%</td>
<td>40.0%</td>
</tr>
<tr>
<td>13-week</td>
<td>-33.9 mm</td>
<td>-45.2%</td>
<td>66.7%</td>
<td>53.3%</td>
<td>33.3%</td>
</tr>
<tr>
<td>26-week (primary)</td>
<td>-40.7 mm</td>
<td>-55.6%</td>
<td>86.6%</td>
<td>66.6%</td>
<td>26.6%</td>
</tr>
<tr>
<td>52-week (n=13)</td>
<td>-36.9 mm</td>
<td>-51.0%</td>
<td>61.5% (53.5%)</td>
<td>53.8% (46.7%)</td>
<td>38.5% (33.3%)</td>
</tr>
<tr>
<td>104-week (n=11)</td>
<td>-42.2 mm</td>
<td>-54.6%</td>
<td>72.7% (53.5%)</td>
<td>63.4% (46.7%)</td>
<td>45.5% (33.3%)</td>
</tr>
</tbody>
</table>
### Roland-Morris Disability Questionnaire

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>AVG Individual Change from Baseline</th>
<th>AVG % Individual Change from Baseline</th>
<th>≥ 30% Improvement (% of Patients)</th>
<th>≥ 50% Improvement (% of Patients)</th>
<th>≥ 75% Improvement (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-week</td>
<td>-2.5</td>
<td>-8.5%</td>
<td>28.6%</td>
<td>26.6%</td>
<td>6.6%</td>
</tr>
<tr>
<td>4-week</td>
<td>-4.9</td>
<td>-27.0%</td>
<td>53.3%</td>
<td>40.0%</td>
<td>20.0%</td>
</tr>
<tr>
<td>13-week</td>
<td>-5.1</td>
<td>-34.1%</td>
<td>66.7%</td>
<td>40.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>26-week (primary)</strong></td>
<td><strong>-6.3</strong></td>
<td><strong>-41.9%</strong></td>
<td><strong>73.3%</strong></td>
<td><strong>53.3%</strong></td>
<td><strong>20.0%</strong></td>
</tr>
<tr>
<td>52-week (n=13)</td>
<td>-9.0</td>
<td>-59.2%</td>
<td>84.6% (73.3%)</td>
<td>61.5% (53.3%)</td>
<td>30.8% (26.7%)</td>
</tr>
<tr>
<td>104-week (n=11)</td>
<td>-9.5</td>
<td>-60.6%</td>
<td>81.8% (60.0%)</td>
<td>72.7% (53.3%)</td>
<td>36.4% (26.7%)</td>
</tr>
</tbody>
</table>
Mechanisms of Discogenic Pain Relief by Heating

• Unclear

• Two hypotheses:
  1. Denervation of the tissue or destruction of the overgrowth of nociceptors
  2. Change the structure of the collagen fibers in the annulus, causing an increase in annular stability

• Histological studies involving IDET did not support these two hypotheses

Denervation

- Number of nerve endings in the experimentally induced annular tear in sheep were counted.
- 18 months after IDET, the number of nerve fibers identified in the posterior annular tear was the same for those specimens that had undergone IDET and those that did not (Freeman et al 2003)
- Irreversible nerve blocks occur at 45 degrees Centigrade in all types of nerve fibers (Smith et al 1981)


History of Treating The Disc with Heat

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.
Temperatures monitoring at designated safety zones outside the disc demonstrated maintenance of near-physiologic conditions while temperature across the posterior annuls reached 65°C.

Petersohn J et al. 2008 Pain Medicine (9): 26-32
Biacuplasty study using explanted human lumbar spines.

Kapural et al. 2008 Pain Medicine (9): 68-75
Cadaver Study

Temperature measured by sensors

Kapural et al. 2008 Pain Medicine (9): 68-75
TransDiscal System During Procedure

Kapural et al. 2008 Pain Medicine (9): 60-67
Final View with Probes
Morphometry of Lumbar Disc

<table>
<thead>
<tr>
<th></th>
<th>L3</th>
<th>L4</th>
<th>L5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc Width</td>
<td>36.0 – 58.4 mm</td>
<td>40.2 – 63.8 mm</td>
<td>40.2 – 70.1 mm</td>
</tr>
</tbody>
</table>

Wider angle of insertion may be necessary for large discs to maintain maximum distance between probes to be 2.5cm – 3cm

Acceptable angle

- Approach angle is adjusted to 45° from the median
- Increased approach angle brings probes close enough to create a confluent lesion
- Set temperature is adjusted to 50 °C
- Following the bipolar lesion, monopolar lesions are created around each electrode to lesion the posterior-lateral aspect of each disc.
Biacuplasty

- Set temperature adjustment to 50°C increases lesion size
  - Max. tissue temperature is 75°C
- Without probe repositioning, additional monopolar lesions created around each electrode to heat posterior lateral region
  
  Kapural et al, 2012

- 45° approach angle
- 50°C set temperature bipolar lesion
- 60°C Monopolar lesions, 2.5min
Randomized Control Trial

• 59 were treated: 29 randomized to IDB and 30 to sham

• The principal outcome measures were physical function, pain, disability, and opioid usage.

Primary Outcomes-Function (SF-36-PF)

SF-36 Physical Functioning (PF)
Oswestry Disability Index (ODI)

<table>
<thead>
<tr>
<th>Time</th>
<th>IDB-PF</th>
<th>Sham-PF</th>
<th>IDB-ODI</th>
<th>Sham-ODI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bsl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3 mo</td>
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<td></td>
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<tr>
<td>6 mo</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

p = 0.029

p = 0.037
Search for an ideal candidate......
A Prospective, Randomized, Multi-Center, Open Label Clinical Trial Comparing Disc Biacuplasty with Medical Management for Discogenic Lumbar Back Pain

a.k.a. The “COLD” TRIAL

Multi-Center, Open-Label Disc Biacuplasty Trial
Study Plan - Global

• 12-month prospective, randomized, open-label, multi-center clinical study.
• Adult subjects with a history of chronic discogenic lower back pain (≥ 6 months) who have been previously unresponsive to conservative therapy are eligible to participate.
• Eligible subjects will be randomized in 1:1 ratio to receive either disc biacuplasty with the TDS (treatment group) or conservative therapy (control group).

• Purpose: The primary objective of this randomized controlled trial is to evaluate the safety and efficacy of the TransDiscal System (TDS) in treating discogenic pain of the lumbar spine using a modified disc biacuplasty procedure. The primary efficacy measure will be the Visual Analog Scale (VAS) at 6 months post treatment/randomization and the TransDiscal System will be compared against medical management (standard of care).
Control Group

- Visit 3 – (Day 0) (Same Day as Visit 2)
- Visit 4 - Post-Treatment Visit (Month 1)
- Visit 5 - Post-Treatment Visit (Month 3)
- Visit 6 - Post-Treatment Visit (Month 6)
- Visit 7 - Follow-up Visit (Month 9)
- Visit 8 - Follow-up Visit (Month 12)

Active Treatment Group

- Visit 3 - Treatment Visit (Day 0)
- Visit 4 - Post-Treatment Visit (Month 1)
- Visit 5 - Post-Treatment Visit (Month 3)
- Optional crossover
  - Visit 6a – Crossover Treatment
    - Visit 6b – Post-Treatment Visit (Month 1)
    - Visit 7 - Post-Treatment Visit (Month 3)
    - Visit 8 - Post-Treatment Visit (Month 6)
- Visit 7 - Follow-up Visit (Month 9)
- Visit 8 - Follow-up Visit (Month 12)

Study Design

Screening Phase Days - 60 to 0

Visit 2 - Randomization Visit

Visit 3a – Phone Call First 20 Subjects in Treatment Group (Day 4)
Outcome Measures

**Primary:**

- Change in average daily pain Visual Analog Scale (VAS) score between Screening and Follow up.

**Secondary:**

- Proportion of subjects with greater than 2 points decrease or 30% drop in average daily pain related VAS score.
- Mean change in score of Short Form 36 (SF-36) from screening to 6 month follow up visit
- Mean change in score of EuroQuol 5d (EQ-5d) between screening and 6 month follow up visit
- Mean change in score of Beck's Depression Inventory (BDI) between screening and 6 month follow up visit
- Mean change in score of Patient Global Impression of Change (PGIC) between screening and 6 month follow up visit
- Mean change in score of Oswestry Disability Index (ODI) between screening and 6 month follow up visit
Exclusion Criteria

1. Evidence of compressive radiculopathy with predominant leg pain
2. Evidence of nucleus pulposus herniation or free disc fragments on MRI
3. Evidence of >2 discs desiccated based on MRI or symptomatic involvement of more than one lumbar disc levels.
4. Asymptomatic disc bulges >5 mm at the treatment level.
5. Prior lumbar surgery of any kind at the treatment level (micro-discectomies and/or minimally invasive procedures at other levels are not excluded)
6. Prior spinal fusion below the T10 level.
Exclusion Criteria - Cont

7. Symptoms or signs of lumbar canal stenosis at any level
8. Evidence of structural abnormality at the lumbar level (except non-symptomatic spondylolysis resulting in spondylolisthesis no more than Grade 1 upon flexion and extension)
9. Any generalized or multifocal pain, conversion or multiple non-anatomical complaints
10. Pending or active compensation claim, litigation or disability income renumeration (secondary gain)
Exclusion Criteria - Cont

11. Chronic pain associated with significant psychosocial dysfunction
12. BDI score >20
13. Current pregnancy, recent delivery (within 3 months of consent) or the intent of becoming pregnant during the study period.
14. Systemic or localized infection at the anticipated needle entry site (subject may be considered for inclusion once infection is resolved)
15. Discitis
16. Allergies to any medication to be used in the procedure
Exclusion Criteria - Cont

17. Present symptomatic lumbar spinal fracture
18. History of uncontrolled coagulopathy, ongoing coagulation treatment or unexplained or uncontrollable bleeding that is uncorrectable
19. Progressive neurological deficits
20. Within the preceding two years, subject has suffered from active narcotic addiction, substance abuse or alcohol abuse
21. Current prescribed opioid medications equivalent to >120 mg of morphine per 24 hours
22. Uncontrolled immunosuppression (e.g. AIDS, cancer, diabetes, etc)
Exclusion Criteria - Cont

23. BMI >32.5 kg/m²
24. Participating in another clinical trial/investigation 30 days prior to signing informed consent
25. Negative or indeterminate lumbar discography results as assessed per ISIS guidelines
26. Subject unwilling or unable to comply with follow up schedule or protocol requirements.
Current Status

- 63 patients enrolled/randomized
- 9 US Locations
- Data analysis complete through 6 months
- Benefits demonstrated for pain/function/QOL
- **SF-36 and ODI showed progressive improvement over 12 months**
- Safety re-confirmed
- Full results released at CCF Symposium (3/2015)
- Manuscript in process
Summary

• Injections into disc are lacking sufficient clinical evidence
• Biacuplasty is an effective minimally invasive alternative for treatment of lumbar discogenic back pain
• Strict selection criteria improves results of biacuplasty
• Fibrin sealant is promising alternative
Thank you