Nonoperative Treatment Modalities for Knee Osteoarthritis

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I have no actual or potential conflict of interest in relation to this program or presentation.
Knee Osteoarthritis: a prevalent disease

- 1/3 of all adults have radiological signs of osteoarthritis
- Knee osteoarthritis affects 6% of all adults
- The prevalence of knee OA in 70- to 74-year-olds is up to 40%.

Clinical Criteria

- Knee pain and **at least three** of the following (95% sensitivity, 69% specificity):
  - Morning stiffness lasting < 30 minutes
  - Crepitus on active motion of the knee
  - > 50 years of age
  - Bony tenderness
  - Bony enlargement
  - No palpable warmth
Imaging

AP or standing extended view (SEV) is common radiographic examination for evaluation of knee OA.
Imaging

Narrowing of the joint space is better visualized in fixed flexion view (FFV) (Duddy et al 2004)

**Difference in joint space width**

<table>
<thead>
<tr>
<th></th>
<th>Medial (SEV–FFV)</th>
<th>Lateral (SEV–FFV)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.8 (1.0)</td>
<td>0.2 (1.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Women</td>
<td>0.7 (0.9)</td>
<td>0.2 (0.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total</td>
<td>0.7 (1.0)</td>
<td>0.2 (1.0)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Average values (SD) in mm.

57-year-old male. A. Standing extended view (SEV) of the right knee. B. Fixed flexion view (FFV) of the right knee. The 30-mm calibration disc has been marked with an asterisk.

Management of Knee Osteoarthritis Overview

- Non-pharmacologic Treatment
- Oral Medications
- Injections
- Surgery
Nonpharmacologic Therapies

- Physical Therapy/ Exercises Programs
- Weight Loss
- Braces
- Transcutaneous Electrical Nerve Stimulation (TENS)
Exercise

- **Land-based therapeutic exercise**
  - Reduced knee pain for 2-6 months after cessation of formal treatment
  - Moderate improvement in physical function
  - Magnitude of the treatment effect comparable with estimates reported for NSAIDs. (Fransen 2015)

- **Aquatic exercise**
  - Moderate improvements in pain, function, and QOL
  - No significant differences between aquatic and land-based exercise on pain, function, or QOL. (Barker 2014)
Weight Loss

- **Obesity**
  - Increased mechanical burden
  - Altered biomechanics

- Reduction reduces OA risks
  - Modest weight loss (5 kg or 5% of body weight) reduced OA by ACR criteria (clinical and radiographic), K&L grades and joint space narrowing ≥ 1.0 mm (Runhaar 2016)
Transcutaneous Electrical Nerve Stimulation (TENS)

- After 3 months of TENS unit use, Knee OA subjects
  - Significant improvement in pain (via reduction of VAS scores)
  - Function
  - Quality of Life
- Adjunct to current nonoperative treatment of knee OA

- Clinically, knee braces w/ TENS have been effective

Braces: Unloader Braces

- “Off loading” = Load redistribution and joint alignment
- Customized knee braces specifically designed to treat OA.
  - Stabilize the joint
  - Reduce intra-articular pain
  - Allows improved function and muscle strengthening
- Adherence Issues secondary to discomfort
Pharmacologic Therapies

- Glucosamine and Chondroitin
- Non-Steroidal Anti-inflammatory Drugs
- Analgesics
  - Tylenol for mild to moderate pain
  - Opioids for moderate to severe pain
A 2015 Cochrane review

- Chondroitin +/- glucosamine, resulted in a statistically significant improvement in pain scores in studies with less than six months of follow-up
- Clinically meaningful, but effect was 8 points on 100-point scale

Chondroitin sulfate and glucosamine vs. Celebrex

- At 6 month follow-up: no difference in pain, stiffness, function, or swelling.

Chondroitin sulfate and glucosamine vs NSAIDs/Tylenol

- After 24 months: GC group had less cartilage loss on medial central plateau
Opioid Abuse/Dependency

- In 2014, 1.9 million had a substance use disorder from prescription pain relievers

- Drug overdose:
  - Leading cause of accidental death in the US
  - 47,055 drug overdose deaths in 2014
  - 18,893 overdose deaths related to prescription pain relievers

- In 2012, 259 million Rx for opioids
  - > 1 bottle for every American adult

Corticosteroid Injections

- Accuracy of injection
- Choice of steroid
- Risks
Can you identify the joint? Hoffa’s fat pad?
Utility of Ultrasound Guidance

- Imaging guidance improved the accuracy of intra-articular injections of the knee (96.7% versus 81.0%, P < 0.001).

- In particular, ultrasound guidance of knee injections resulted in better accuracy than anatomical guidance (95.8% versus 77.8%, P < 0.001).

# Intra-articular Effect on OA

**TABLE 1**

Corticosteroid Preparations

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Preparation</th>
<th>Solubility (in water)</th>
<th>Intra-articular Action Duration, d</th>
<th>Clinical Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>Hydrocortisone acetate (HCA)</td>
<td>Insoluble</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Methylprednisolone acetate (MPA)</td>
<td>Insoluble</td>
<td>7</td>
<td>10-30</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Dexamethasone sodium phosphate (DSP)</td>
<td>Soluble</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone (DEX)</td>
<td>Insoluble</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>Betamethasone acetate (BMA)</td>
<td>Insoluble</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Prednisolone</td>
<td>Soluble</td>
<td>10</td>
<td>10-30</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Triamcinolone acetonide (TA)</td>
<td>Insoluble</td>
<td>14</td>
<td>10-40</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone hexacetonide (THA)</td>
<td>Insoluble</td>
<td>21</td>
<td>20</td>
</tr>
</tbody>
</table>

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**Chloe Werneck**, BS, [Hillary J. Braun, BS,](#) and [Jason L. Dragoo, MD](#)† **The Effect of Intra-articular Corticosteroids on Articular Cartilage:** A Systematic Review. Orthop J Sports Med. 2015 May; 3(5):
Deleterious Effects

Chondrocyte viability after 14 days

Aside from glucocorticoids, what intra-articular pharmacotherapy alternatives are available?
Hyaluronic Acid Injections
Hyaluronic Acid (HA)

- Articular cartilage consists on chondrocytes, a pericellular matrix (PCM), and the extracellular matrix (ECM).
  - ECM = collagens & proteoglycans.
  - Proteoglycans = Glycoaminoglycans (GAG) chains covalently linked to proteins.
  - Hyaluronan is an anionic GAG found in connective tissues.

- Synvisc-One® (hylan G-F 20)
  - Elastoviscous high molecular weight fluid containing chemically crosslinked hylan A and hylan B polymers.
  - Produced from chicken combs.
Hyaluronic acid (n=312 patients) vs Corticosteroids (n=294 patients) for knee OA. (Bannuru et al. 2009)

- Weeks 0-4: Intra-articular corticosteroids > HA
- Weeks 4-8: Comparable
- Weeks 8+: Intra-articular corticosteroids < HA

HA relieves the symptoms of OA, modify the structure of the disease joint, and the rate of OA disease progression. (Goldberg 2005)
**Hyaluronic acid vs NSAIDs** (n=712 patients) for knee OA. (Bannuru et al. 2014)
- IAHA is not significantly different from continuous oral NSAIDs at 4 and 12 weeks.

**Hyalgan** (n=165) vs saline (n=170) for knee osteoarthritis. (Jorgensen 2010)
- At 3 months, 53 (HA) and 47 (saline) patients did not respond to treatment.
- Mean time to recurrence: 172 days (HA) and 204 days (saline)
- No difference between HA and saline group.
Systematic reviews and a meta-analysis by Rutjes (2012) and Samson (2007) → questionable clinical benefit

- Variable quality of trials
- Potential publication bias
The American Academy of Orthopaedic Surgeons (AAOS) does not support the use of viscosupplementation for treatment of knee OA.
Do Injections Work For Knee Pain? Don't Waste Your Money
Platelet Rich Plasma (PRP)
Hines Ward

- 4x Pro-Bowl selection
- Steelers All-time Leader in receptions, receiving yards, and receiving TDs
Brandon Roy

- NBA Rookie of the year (2007)
- PRP injections for hamstrings and knees
Troy Polamalu

- 7-time Pro Bowler
- 2010 NFL Defensive Player of the Year
Tiger Admits to Platelet-Rich Plasma Therapy, What's That?

By LAUREN COX
April 7, 2010
PRP effective?

"The temptation of it is that you're using your own tissue, your own blood to heal your injury. But the process? I'm just not sure it's ready to go yet...Some people have had good luck with it, and I don't know if it's real or not"

What is PRP?

- **Platelet-rich plasma (PRP)** is concentrated autologous platelets after centrifugation of whole blood plasma.
  - Platelets activated by thrombin and calcium chloride → release of growth factors and cytokines
  - Growth factors and cytokines → healing of bone and soft tissue.
Platelet-rich Plasma

- Theoretical Effect of PRP on OA
  - Proliferation of autologous chondrocytes and MSC
  - Reduction in interleukin (IL)-1 beta-induced inhibition of type II collagen/aggreccan gene expression
Treatment of Knee Joint Osteoarthritis with Autologous Platelet-Rich Plasma in Comparison with Hyaluronic Acid

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At 6 month follow-up:

**PRP: 18.85 (+/- 14.09) vs. HA: 30.9 (+/- 16.6)**
At 6 months followup:
PRP: 2.69 (+/- 1.9) vs HA: 4.3 (+/- 2.1)
PRP vs Placebo injections

- ACP (n = 15) or saline placebo (n = 15) for a series of 3 weekly injections.
- WOMAC scores served as the primary efficacy outcome measure.
- Patients were followed for 1 year.
- No statistically significant difference in baseline WOMAC scores between the 2 groups.

At the study conclusion (12 months), subjects in the ACP group had improved their overall WOMAC scores by 78% from their baseline score

- 7% for the placebo group
Advantages

- Platelet-rich preparations are easily obtained after a simple centrifugation process.
- Clinical efficacy can be expected with a minimum increase in platelet concentration of 4- to 6-fold.
- PRP is prepared from autologous blood
  - No concerns of allergic reactions or disease transfer
- PRP does not promote hyperplasia, carcinogenesis, or tumor growth
Cryoneurolysis

- Targeted cold to a peripheral nerve which immediately prevents the nerve from sending pain signals.
- The effect on the nerve is temporary and does not cause permanent damage.
  - Structural components of the nerve remain.
**VAS Pain Score**

- **Mean**
- **Median**

**Duration of Treatment Effect**

<table>
<thead>
<tr>
<th>Days after Treatment</th>
<th>Percentage of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>100%</td>
</tr>
<tr>
<td>30</td>
<td>80%</td>
</tr>
<tr>
<td>56</td>
<td>60%</td>
</tr>
<tr>
<td>84</td>
<td>40%</td>
</tr>
<tr>
<td>112+</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Note: Subjects reporting effective 50% pain relief are measured beyond that point.*
Other investigational agents

- **Bisphosphonates**
  - Theory: target subchondral bone turnover and synovitis
  - Largest RCT, Risedronate vs Placebo
    - More improvement of pain and function in placebo group

Sprifermin

- Injectable recombinant human fibroblast growth factor 18
- Theory: promotes chondrogenesis, cartilage matrix formation, and cartilage repair
- Proof of concept study of 180 patients
  - No significant changes in medial compartment cartilage thickness at 6 or 12 months

“Arthroplasty is not a disease-modifying procedure but rather is a mechanical solution to a biologic problem“

Questions?