Non-Operative Options for Articular Cartilage Issues in the Athlete’s Knee

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OBJECTIVES

• Review the function of articular cartilage
• Examine the most recent update on OARSI guidelines
• Review the clinical role of HA as a treatment for osteoarthritis
• Consider the role of bracing
• Investigate role of other novel treatment approaches in OA
Why is this important?

• High prevalence of osteoarthritis
• Our patients look to us to help them manage pain and restore/preserve function
• Our job is to balance safety and efficacy
Scope of the Problem: an example

- Increasing number of ACL tears, especially in women
  - Before 1972, <300K female athletes
  - 250K ACL/yr in US
  - 50% develop OA after 10-15yrs (Lohmender AJSM 2007)
Articular Cartilage Function

- Distribute load
- Minimize peak stress
- Low friction surface
Osteoarthritis
CLINICAL MANAGEMENT
OA Treatment Modalities

OARSI GUIDELINES – Nonpharmacologic Therapy

- Patient education (small effect pain + function)
- Self-management programs (small effect pain + function)
- Weight reduction (improve pain + function)
- Acupuncture (improve pain + function + stiffness)
- Exercise (strengthening, aerobic, water-based)
  - Improve pain and function

Acetaminophen * (<3g/day) - ↓ pain but not function

NSAIDs (weigh risk/benefit)/short course

Topical NSAIDs (better safety profile)
  - Effect pain + function + stiffness

IA corticosteroid (↓ pain but not function/stiffness)

Glucosamine sulfate (↓ pain)

### Relationship between ES for pain relief and quality of randomized controlled trial

<table>
<thead>
<tr>
<th></th>
<th>All trials ES (95% CI)</th>
<th>High quality trials (Jaded =5), ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture</td>
<td>0.35 (0.15,0.55)</td>
<td>0.22 (0.01,0.44)</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>0.14 (0.05,0.23)</td>
<td>0.10 (-0.03,0.23)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>0.29 (0.22,0.35)</td>
<td>0.39 (0.24,0.55)</td>
</tr>
<tr>
<td>Topical NSAIDs</td>
<td>0.44 (0.27,0.62)</td>
<td>0.42 (0.19,0.65)</td>
</tr>
<tr>
<td>Glucosamine Sulfate</td>
<td>0.58 (0.30,0.87)</td>
<td>0.29 (0.003,0.57)</td>
</tr>
<tr>
<td>Chondroitin Sulfate</td>
<td>0.75 (0.50,1.01)</td>
<td>0.005 (-0.11,0.12)</td>
</tr>
</tbody>
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The Role of Bracing

• Valgus unloader braces for medial compartment knee OA
  – Reduce knee adduction angle measures
  – Improve measures related to medial knee joint loading
  – Improve gait symmetry and speed
    • Benefits in walking, running, stairs
  – Above in middle-aged athlete- no studies in young, athletic OA patients

Viscosupplementation

- The use of intraarticular viscosupplementation, or hyaluronic acid (HA), injections in pain management in osteoarthritis has been established
  - OARSI ES significant for improving pain and function
Background

• Normal human knee contains about 5-8mg hyaluronic acid in 2ml of synovial fluid.
• In arthritic knee the amount of HA is diminished, reducing the viscoelastic property of the synovial fluid.
• This in turn increases the stress and shear forces experienced by the articular surface and may lead to further damage.
Hyaluronic acid has both anti-inflammatory and analgesic properties.

- It has been shown to inhibit macrophage phagocytosis and neutrophil adherence.
- It also reduces release of arachidonic acid (a precursor of inflammatory mediators) from fibroblasts in the synovium.
- The analgesic effects of HA include possible direct inhibition of pain receptors.
- It purportedly also indirectly binds substance P, thereby decreasing pain signals.
HA- Properties

• Demonstrates several properties that lead to its effectiveness and tolerability.
• Displays remarkable lack of immunogenicity helping limit the chance of local reaction after intraarticular injection.
• In the joint exhibits passive diffusion in synovial fluid and prolonged half-life within the synovium.
Indications for Viscosupplementation in OA

- Failure to respond to conventional nonpharmacologic therapy
- Inadequate response to simple analgesics
## Viscosupplements

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Molecular Weight (kDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyalgan</td>
<td>500-730</td>
</tr>
<tr>
<td>Synvisc</td>
<td>6000</td>
</tr>
<tr>
<td>Supartz</td>
<td>620-1170</td>
</tr>
<tr>
<td>Euflexxa</td>
<td>2400-3600</td>
</tr>
<tr>
<td>Orthovisc</td>
<td>1000-2900</td>
</tr>
</tbody>
</table>
No Consensus Regarding Importance of MW and Origin of HA

- RPB study comparing low, middle, and high MW
- No difference in pain outcomes
- Slightly higher incidence of local adverse events in Hylan-GF (high MW) group with repeat course
Dosing

- Usually 3 or 5 weekly injections
- Single injection (combined doses)
- Repeat series if at least 6 mos of symptom improvement
Adverse Reactions

- Side effects of intraarticular viscosupplementation with HA occur at a rate of about 1% per injection.
- Local reactions such as warmth, swelling and pain can last 1-2 days.
- Granulomatous inflammation arising within 48 hours after injection has occurred with Hyalan-GF. This adverse effect typically has been shown to resolve in 1-2 weeks.
Clinical Results

• Improvement in pain, function, and patient global assessment
• Pain improvement in studies followed up to 26 wks (especially in 5 to 13 wk period)
• ? benefit using post-op (decreased chondrocyte apoptosis)
• The salutary effects seem to be better than intraarticular corticosteroid injection in the intermediate term.
HA vs IA corticosteroi whole

Favors
Hyaluronic acid

Relative Effect Size

Favors
Corticosteroids

Time Points (weeks)

5 Trials
N_HA = 250
N_CS = 234
I^2 = 47%

7 Trials
N_HA = 307
N_CS = 288
I^2 = 37%

3 Trials
N_HA = 193
N_CS = 176
I^2 = 49%

4 Trials
N_HA = 205
N_CS = 184
I^2 = 0%

HA – Hyaluronic acid
CS – Corticosteroid
Summary of Viscosupplements for OA

- They don’t “restore” cartilage, but do they slow progression of OA?
- Have a role in pain management in osteoarthritis
- Little difference between brands
- Possible suppression of catabolic enzymes that attack joint cartilage
Other Novel Treatment Options for OA?
Bisphosphonates?!

- In treatment algorithm for osteoporosis
- Why use for (knee) OA?
  - ? modify turnover of subchondral bone
  - ? ↓ sensitization/activation of nerve channels at subchondral junction → pain modulation
Bisphosphonates?

- Meta-analysis of 2 largest knee OA studies
- Risedronate 5mg daily or 15mg weekly
- No significant difference from placebo in WOMAC scores

*PLoS One.* 2013 Sep 4;8(9)
Platelet rich plasma

• Concept:
  • Growth factors mediate the biological process of repair
  • Individual growth factors have been shown to enhance injury repair in animal models
  • Increased amount of growth factors → healing may be accelerated or enhanced (repaired tissue more approximates original tissue)
Platelet rich plasma

- Platelets: one of the first cells to arrive at location of injury; filled with growth factors and other cells:
  - Platelet-derived growth factor (PDGF)
  - Transforming growth factor (TGF-B)
  - Insulin-like growth factor (IGF)
  - Epidermal growth factor (EGF)
  - Vascular endothelial growth factor (VEGF)
  - Fibroblast growth factor (FGF)
PRP and Cartilage: rationale

- Milieu of bioactive anti-catabolic and anabolic molecules that modify the arthritic process
  - Subchondral bone
  - Cartilage
  - MSCs
  - Synovium

Boswell, Fortier, Cole, Arthroscopy 2011
Platelet-Rich plasma: Preparation

- Draw 30-100 mL venous blood
- Mix with anticoagulant
- Centrifuge 15-20 min at 3500-4000 RPM
- Separate layers
- Yields 3-10 mL of PRP at about 3-7x baseline platelet concentration

- Multiple variables in preparation
PRP: role in cartilage repair mechanism of action

- Unclear mechanism by which PRP interacts with cartilage
- PRP has been shown to have anti-inflammatory effect on chondrocytes
PRP: role in cartilage repair in vitro studies

- Anitua (*Rheumatology*, 2007)
  - Application of PRP can improve the quality of synovial fluid by inducing the endogenous secretion of hyaluronic acid by synovial cells
• 100 consecutive patients with low degree of articular degeneration of the knee (level 4)
• 3 PRP injections (no control group)
• 6 months: pain and function significantly better
• 12 months: pain and function significantly worse than at 6 months (but still significantly better than at baseline)
• Trend toward better results in young men, low BMI, less severe cartilage lesions
Cartilage Lesions


Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis.

Filardo G, Kon E, Buda R, Timoncini A, Di Martino A, Cenacchi A, Fornasari PM, Giannini S, Marcacci M.

Biomechanics Laboratory-III Clinic, Rizzoli Orthopaedic Institute, Via Di Barbiano 1/10, 40136, Bologna, Italy. g.filardo@biomec.iir.it

• Same series of patients as previous study by Kon
• Continued worsening of clinical outcome scores at 24 months (IKDC, EQ VAS)
• Satisfaction rate remained the same at 12 and 24 months (80%)
• Better results in younger patients, more mild disease
Cartilage lesions
PRP vs hyaluronic acid


Sánchez M, Anitua E, Azofra J, Aguirre JJ, Andia I.
Unidad de Cirugía Artroscópica "Mikel Sanchez", Vitoria, Spain.

• Retrospective cohort study (Level 3)
• 30 patients in each group (PRP vs hyaluronic acid)
• 3 injections (weekly)
• Pain scores 5 weeks after treatment
• Decreased pain and enhanced function after injection of PRP compared to hyaluronic acid
Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial

Filardo et al
BMC Musculoskelet Disord. 2012 Nov 23;13:229
PRP and Cartilage

- PRP decreases pain without tissue regeneration
- PRP increases HA synthesis
- Superior to HA? Corticosteroids?
- Promote as first line therapy?
- Timing/dosage/prep TBD
Wait a minute…

“It should be clear that good quality comparative clinical studies are sorely needed for all the possible tissues and pathologic conditions that might be addressed with PRP or similar reparations.”

• Bruce Reider MD AJSM editor 2009
“PRP treatment should only be indicated for low-grade cartilage degeneration and in case of failure of more traditional conservative approaches”

Need more studies controlling for the many variables---- not one size fits all
• Diekman- “Several recent studies have greatly advanced the development and preclinical evaluation of potential stem cell-based treatments for osteoarthritis through novel approaches focused on cell therapy, tissue engineering and drug discovery.”
“FUNKY TREATMENTS IN ELITE SPORTS PEOPLE: DO THEY JUST BUY REHABILITATION TIME?”

-Jill Cook
Take-aways for treatment of knee OA

• Non-pharmacologic and pharmacologic options exist for improving pain and function
• Bracing may have a place in unicompartmental disease
• IAHA are helpful
• PRP may be helpful in low grade DJD
• Taking the right clinical message from research
Thank you!