Non op Treatment of Ankle OA

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Financial Disclosure

- SAB for BMTI, Tissuegene, DJ Ortho
- Founder Cre Osso
- No financial conflict with this talk
Outline

- Clinical impact of ankle OA
- Need for Non-Op Care
- Option: Modalities and Bracing
  - Options: Pharmacologic
    - Chondroitin sulfate
    - PRP
    - Corticosteroid
    - Hyaluronic Acid
Impact End-stage Ankle Arthrosis
Glazebrook et al JBJS 2008

Comparison of Health-Related Quality of Life Between Patients with End-Stage Ankle and Hip Arthrosis

By Mark Glazebrook, PhD, MD, FRCS(C), Tim Daniels, MD, FRCS(C), Alastair Younger, MSc, MD, FRCS, CJ. Foote, BSc, Murray Penner, MD, FRCS(C), Kevin Wing, MD, FRCS(C), Johnny Lau, MSc, MD, FRCS(C), Ross Leighton, MD, FRCS(C), and Michael Dunbar, PhD, MD, FRCS(C)

Investigation performed at Dalhousie University/Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada, St. Michael’s Hospital, Toronto, Ontario, Canada, University of British Columbia, Vancouver, British Columbia, Canada, and Memorial University/St. John’s Health Science Centre, St. John’s, Newfoundland, Canada

Background: End-stage ankle arthrosis is one of the leading causes of chronic disability in North America. Information on this condition is limited. The amount of pain and the reduction in health-related quality of life and function have not been quantified with use of universal outcome measures. The purpose of the present study was to compare the extent of pain, loss of function, and health-related quality of life in two cohorts of patients waiting for the surgical treatment of end-stage ankle or hip arthrosis.
Clinical impact
Number of Cases in US

75-100K Ankle fusion annually
6-8000 TAA
Need for Non-Operative Care - Ankle OA

Medical issues (cardiac, pulmonary)
Mentally unstable
Unable to comply with protocol
Soft Tissue envelope
Underlying infection
Inappropriate age for TAA or arthrodesis
What do we want? TIME
What can we do to buy time?
Recommendations for Managing OA

PT Alternative Modalities

- **Therapy**: cold or hot or contrast-locally applied
- **Therapeutic US**: high frequency mechanical vibration
- **Electronic TENS**: e-current transmitted via electrode to specific muscle to stimulate motor units ref27
- **Low level laser therapy**: single wavelength of light to cause photo reaction

- Absence of RCT for therapy, therapeutic US, TENS or laser therapy alone in Ankle OA to show a significant effect
NO LOVE – Just DATA in RA

RCT-low quality evidence

Therapeutic US has effect of decrease painful joint score and increase function
TENS-conflicting
REF 28,31
NO LOVE – Just DATA in RA

Laser therapy
Three RCT-improvement in pain score
Two RCT-increase motion or flexibility
But why or how?
REF 32
Orthoses and Shoe modifications

**PRO:**
- Pain relief
- Improve quality of life
- Postpone TAR or AA

**CONS:**
1. Custom made $$$$$
2. Rigid hindfoot deformity—often hard to tolerate brace
3. Need for patient compliance
4. Not cosmetically appealing
Shoewear modification

SACH Heel:
Shock absorption heel
or

Cushion heel

Application rocker bottom to facilitate fluidity of gait
Shoe modification
In asymmetry ankle joint OA:
Add a medial or lateral wedge to unload OA joint
For severe OA, off the shelf lace-up type athletic brace to Arizona brace to custom rigid AFO
DATA

- Direct Comparison of Individual Orthotic Design is lacking....

- **BUT biomechanical data does exist** (Ref 38)

- **GOALS:**
  - decrease in ankle motion
  - Aids in transition of heel strike to push off during level walking
Three design data
Rigid hindfoot orthotic ie UCBL

Restraints of ankle-hindfoot motion, while allowing forefoot motion
Three design data

Articular hindfoot
AFO orthotic

May be ineffective to limit hindfoot motion but allow forefoot motion REF 35
Three design data

Custom AFO/Shoe

Significant decrease pain
Increase step length and stride length
Reduction of energy expenditure
Ref 39
Pharmacological options

- ORAL Chondroitin sulfate/Glucosamine
- PRP
- Corticosteroid
- Hyaluronic Acid
Oral Chondroitin Sulphate/Glucosamine
Treatment Strategy-Mild Knee OA

- Alternative Medicine
  - May ease symptoms, improve attitude
  - Will not cure acute illness or replace proven medical treatments
- Exercise
- Weight reduction
- Physical/occupational therapy
- Nutraceuticals
  - Glucosamine
  - Chondroitin Sulphate
Use of Glucosamine and Chondroitin Sulfate in the Management of Osteoarthritis

Andrew A. Brief, MD, Steven G. Maurer, MD, and Paul E. Di Cesare, MD

- Improved pain, tenderness, mobility, and sustained relief after discontinuation
- Low side affect profile - mostly gastrointestinal distress
- Many studies inadequate
  - Route, dose, purity, lack of adequate controls in some studies

No data exist for effectiveness of oral chondroitin sulfate/glucosamine for treatment of ankle OA!!
II: Treatment Strategy-Moderate OA

NSAIDs & Steroid

- Aspirin
- Ibuprofen
- Naproxen
- COX-2
Treatment Strategy-Moderate OA

NSAID Facts:

- Causes hypertension
- Only 1 in 5 who have a serious problem from NSAIDs have warning symptoms
- Non-selective NSAIDs account for at least 16,500 deaths and 103,000 hospitalizations annually in the U.S.
- Four times more Americans die from NSAIDs annually than from cervical cancer
- Approximately the same number of Americans die from NSAID toxicity as die from AIDS each year
- Clinically important UGI events occur in 3-4.5% of regular NSAID takers
- In North America, the economic consequences of NSAID use results in $0.66 to $1.25 spent on UGI toxicities for each dollar spent on NSAIDs

Treatment Strategy-Moderate OA

Systemic Considerations of NSAIDs:

Corticosteroid
Steroid Injections

- Pain relief within 24-48 hours\(^1\)
- Lasts up to 6 weeks (short lived)\(^1\)
- Safe before TKA (severe OA)\(^2\)
- Crystalline form (triamcinolone) is more effective than hydrocortisone acetate.\(^1\)
- No more than 4 injections/year\(^3\)
- Can increase hepatic glucose synthesis and antagonize insulin effects\(^4\)

KEY QUESTION of Corticosteroids: Pain relief now at the expense of cartilage later?

- Studies indicate steroid injections can result in chondrotoxicity
  - “Corticosteroids alter the differentiated phenotype of articular chondrocytes”¹
  - “Lidocaine Potentiaties the Chondrotoxicity of Methylprednisolone”²

² Seshadri V, Coyle CH, Chu C. Arthroscopy. 2009;24:337-347.
Concerns of intra-articular steroid raised since 1966-1975
Local intra-articular Steroid
Mechanism of Action

1. Catabolic activity
2. Decrease inflammation
3. Alter micro-environment of joint (i.e. inflammatory cytokines)
Potential Concerns

1. Tendon rupture
2. Skin Discoloration
3. Fat thinning
4. Cartilage degeneration
5. Rare-steroid psychosis
6. Exacerbation of DM
Example of Fat pad atrophy
Literature of Efficacy of local steroid in OA of ANKLE? NO?
But in the knee? YES!
KEY QUESTION: Do repeated local steroid injection have any serious clinical effect on cartilage?

Article exists that patient may have repeated steroid shots

- Creamer P Intra-articular corticosteroid treatment in osteoarthritis Curr Opin Rheumatol 11:417-421, 1999)ref21
Personal Recommendation for use of local steroid for ankle OA

1. Useful not only as **therapeutic** but also as diagnostic test
2. Local intra-articular steroid in ankle may last 4-8 weeks- repeat
3. Avoid same spot for injection to avoid skin effects
III. What do these Athletes have in common?
Both attribute their success to PRP!!
Platelet rich plasma
Autologous Platelet Concentrate

When Activated, Platelets Release Growth Factors

Growth Factors in Platelets

- Platelet Derived Growth Factor (PDGF)
- Transforming Growth Factor-β (TGF-β)
- Vascular Endothelial Growth Factor (VEGF)
- Epidermal Growth Factor (EGF)
- Insulin-like Growth Factor (IGF)
Indication of PRP in Ankle OA or even Foot Ankle surgery: still unknown!

- PRP for Foot Ankle Pathology: systemic review 2013
- Systematic search of Pub Med-17 studies
- Achilles tendon(9)
- Plantar fascia(2)
- Talar OCD(3)
- TAA(2)
- Fusion(1)

No study exists on the use of PRP in ankle OA!
IV. ROLE of Hyaluron Acid injection?
Hyaluronic Acid
Where does hyaluronic acid come from?

YES? Well no!!!

YES!!!!
Joint injection with hyaluronic acid were approved for treatment of knee OA in 1997.
Many brands- **NONE** are FDA approved for ankle OA
280 million injections and over 20 years of use worldwide\(^1\)

More than 20 prospective clinical trials in the published literature\(^2\)

# Characteristic of 5 Common Hyaluronans

<table>
<thead>
<tr>
<th>Product</th>
<th>Origin (method of production)</th>
<th>Molecular weight (kd)</th>
<th>Amount per injection (ml)</th>
<th>Active ingredients per injection</th>
<th>Number of injections per cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hylagan</td>
<td>Rooster combs (naturally derived)</td>
<td>500–730</td>
<td>2</td>
<td>20 mg sodium hyaluronate</td>
<td>3 or 5 weekly</td>
</tr>
<tr>
<td>Supartz</td>
<td>Rooster combs (naturally derived)</td>
<td>620–1170</td>
<td>2.5</td>
<td>25 mg sodium hyaluronate</td>
<td>5 weekly</td>
</tr>
<tr>
<td>Orthovisc</td>
<td>Rooster combs (naturally derived)</td>
<td>1000–2900</td>
<td>2</td>
<td>30 mg sodium hyaluronate</td>
<td>3 or 4 weekly</td>
</tr>
<tr>
<td>Synvisc</td>
<td>Rooster combs (chemically modified or cross-linked)</td>
<td>80%: 6000; 20%: &gt;6000</td>
<td>2</td>
<td>16 mg sodium hyaluronate derivative</td>
<td>3 weekly</td>
</tr>
</tbody>
</table>
HA: Proposed Mechanism of Action

**Protection**
- Protects cells, tissues and pain receptors, thereby reducing pain during normal movement\(^1\)-\(^3\)

**Stimulation**
- HA naturally relieves knee pain and patient can become more active
- A more active patient coupled with the proposed stimulation of HA by synoviocytes can provide pain relief well beyond the presence of exogenous HA in the treated knee\(^4\)-\(^6\)

**Inhibition - Diverse Inflammatory Processes**
- HA inhibits IL-1\(\beta\) (interleukin 1 beta, inflammatory cytokine), NO (nitric oxide, free radical) & MMP-3 (matrix metalloproteinase-3, degradative enzyme) pathways which prevents further metabolic breakdown\(^7\)-\(^9\)

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The strenuous-running animal model of OA

Controls did not receive injections

Hyluronic

6-week strenuous-running model, small animals

Cartilage lesion in control animal

6-week strenuous-running model, small animals

Cartilage protection in HA animal study

6-week strenuous-running model, small animals

Salk et al JBJS 2006

Randomized double blinded controlled

Efficacy and safety of five weekly injection of low MW non cross linked HA vs saline

20 patient randomized in two groups

a. HA
b. Saline

17 were followed

Results:

active and placebo shows improvement in AOS and VAS at 3 and 6 months but

NO DIFFERENCE Between GROUPS
Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Hyaluronic Acid (N = 9)</th>
<th>Placebo (N = 8)</th>
<th>Total (N = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57.8 (14.7)</td>
<td>60 (13.9)</td>
<td>58.8 (14.4)</td>
</tr>
<tr>
<td>Female:Male ratio (no. of patients)</td>
<td>5:4</td>
<td>5:3</td>
<td>10:7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 (11.9)</td>
<td>168 (11.4)</td>
<td>169 (11.5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85.5 (24.0)</td>
<td>89.5 (25.9)</td>
<td>87.4 (24.2)</td>
</tr>
<tr>
<td>Affected side (no. of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Right</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

*The data are given as the mean, with the standard deviation in parentheses.*
Fig. 3
Illustration showing the scores for the SF-12 general health questionnaire domains at six months.
Background: Intra-articular injections of hyaluronans have been shown to be safe and effective for the treatment of pain associated with osteoarthritis of the knee. This pilot study was undertaken to gather preliminary data on the efficacy and safety of five weekly intra-articular injections of Hyalgan (sodium hyaluronate; molecular weight, 500 to 730 kDa) as compared with saline solution for the treatment of pain associated with osteoarthritis of the ankle.

Methods: Twenty patients at two test sites were randomized with use of a double-blind (blinded observer), saline solution-controlled, parallel experimental design. Patients were randomized to receive five weekly intra-articular injections of either 1 mL of sodium hyaluronate (10 mg/mL) or 1 mL of phosphate-buffered saline solution into the ankle joint. The primary outcome measurement was the ankle osteoarthritis score. Several secondary outcome measures also were assessed.

Results: Significant improvement in the mean ankle osteoarthritis score from baseline was seen at all follow-up visits from one to six months in both the sodium hyaluronate group and the saline solution group (p < 0.0001). In addition, five of nine patients in the sodium hyaluronate group had >30 mm of improvement in this score, compared with one of eight patients in the control group. No withdrawals were directly attributable to the injections of sodium hyaluronate or saline solution, and no severe medication-related adverse events were observed.

Conclusions: The present study suggests that five weekly intra-articular injections of sodium hyaluronate (molecular weight, 500 to 730 kDa) are well tolerated, can provide sustained relief of pain, and can improve function in patients with osteoarthritis of the ankle. These findings are consistent with those of previously published studies involving intra-articular injections of sodium hyaluronate in other joints, but they require confirmation in a large, randomized, saline solution-controlled study.

Level of Evidence: Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.
Summary of Salk 2006

- active and placebo shows improvement in AOS and VAS at 3 and 6 months but

- NO DIFFERENCE Between GROUPS
Mean Ankle Osteoarthritis Score

![Bar chart showing the mean ankle osteoarthritis score over six months of follow-up.](chart_image.png)

Fig. 1
Illustration showing the mean ankle osteoarthritis score over six months of follow-up.
Efficacy and safety of five weekly injection of low MW non cross linked HA vs. saline

Safety and Efficacy of Intra-articular Sodium Hyaluronate (Hyalgan®) in a Randomized, Double-Blind Study for Osteoarthritis of the Ankle

Michael M. Cohen, DPM; Roy D. Altman, MD; Richard Hollstrom, DPM; Claire Hollstrom, DPM; Craig Sun, DPM; Brad Gipson, DPM

Miami, FL
HYL vs Control

Table 1: Demographics and baseline characteristics (Safety Population)

<table>
<thead>
<tr>
<th></th>
<th>HYL (n = 15)</th>
<th>Control (n = 13)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>56.2 ± 15.1</td>
<td>43.4 ± 14.9</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Men (n, %)</td>
<td>14 (93%)</td>
<td>11 (85%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Body mass index, kg/m² (mean ± SD)</td>
<td>30.5 ± 5.3</td>
<td>29.5 ± 4.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Right ankle involvement (n, %)</td>
<td>10 (67%)</td>
<td>7 (54%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>History of trauma (n, %)</td>
<td>11 (73%)</td>
<td>10 (77%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Kellgren-Lawrence grade (mean ± SD)</td>
<td>2.8 ± 1.2</td>
<td>2.8 ± 0.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Signal ankle range of motion (degrees ± SD)</td>
<td>19.0 ± 9.1</td>
<td>21.8 ± 11.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>AOS pain (mean ± SD)</td>
<td>58.8 ± 16.3</td>
<td>51.9 ± 14.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>AOS disability (mean ± SD)</td>
<td>69.4 ± 12.1</td>
<td>52.9 ± 18.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>AOS total (mean ± SD)</td>
<td>64.1 ± 12.8</td>
<td>52.5 ± 14.6</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>WOMAC pain (mean ± SD)</td>
<td>53.4 ± 16.6</td>
<td>45.9 ± 17.3</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>WOMAC stiffness (mean ± SD)</td>
<td>62.7 ± 18.9</td>
<td>65.0 ± 21.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>WOMAC function (mean ± SD)</td>
<td>55.9 ± 15.6</td>
<td>43.6 ± 19.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>WOMAC total (mean ± SD)</td>
<td>55.9 ± 15.1</td>
<td>45.9 ± 17.5</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

AOS = Ankle Osteoarthritis Scale; n.s. = not statistically significant; WOMAC = Western Ontario and McMaster Universities.
Fig. 1: Percent improvement (± standard error) from baseline in AOS total score at Week 2, Week 6, Month 3, and Month 6 after completion of a treatment course with 5 injections of HYL (n = 13) or control (n = 11). P values for the HYL versus control were calculated based on the Wilcoxon rank sum test.
Summary

- Results:
  - Both active and placebo shows improvement in AOS up to 6 months

- NO DIFFERENCE Between GROUPS at 2 and 6 weeks
- At 3 months, AOS score in active was better  BUT
- At six months, no significant difference between group
Null Hypothesis: HA is not superior to saline solution injection
Level 1 HA vs Saline

**AOFAS SCORES**

- **Supartz**
- **Saline**

<table>
<thead>
<tr>
<th>Time</th>
<th>Supartz</th>
<th>Saline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td>0.270</td>
</tr>
<tr>
<td>6 Weeks</td>
<td></td>
<td></td>
<td>0.196</td>
</tr>
<tr>
<td>12 Weeks</td>
<td></td>
<td></td>
<td>0.897</td>
</tr>
</tbody>
</table>
PROBLEMS with DeGroot et al 2012

1. Single injection of low MW
   Other studies were five weekly shots

2. Low MW when higher MW exists
   620K- 1.1million Da

3. Strong placebo effect
Level 1 HA vs Exercise

Intra-articular hyaluronic acid compared to exercise therapy in osteoarthritis of the ankle. A prospective randomized trial with long-term follow-up

V. Karatosun, B. Unver, A. Ozden, Z. Ozay, I. Gunalı

Abstract

The goal of this study has been to determine whether hyaluronic acid (HA) or exercise therapy can improve functional parameters in patients with osteoarthritis (OA) of the ankle.

Methods

In a prospective clinical trial, 43 ankles (30 patients) with radiographic Kellgren Lawrence grade III OA were randomized to receive three intra-articular HA injections, with one-week interval of exercise therapy for six weeks. Patients were evaluated by the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale and followed-up after 12 months.

Results

Total AOFAS Ankle-Hindfoot score of OA patients has improved in both groups, varying from 61.6±16.8 to 90.1±9.7 with HA treatment and from 72.1±16.6 to 87.5±17.5 using exercise therapy at the end of the trial (p<0.01). There were no statistically significant differences between the groups.

Conclusions

This prospective randomized trial confirmed that, both HA injections and exercise therapy provide functional improvement. However, larger trials with longer follow-up are necessary for more definite conclusions.
No difference in pain during activity and pain at rest between local HA and exercise.
No difference in parameters of gait and sagittal motion between local HA and exercise
No difference in parameters between local HA and exercise

- As a result, we conclude that both HA and exercise therapy are effective in alleviating the symptoms of OA and postponing definitive surgeries (total ankle replacement or arthrodesis) for 12 months, increasing the satisfaction levels of the patients.

- However, in our opinion, larger trials with longer follow-up and with cost effectiveness analyses are necessary for more definite conclusions.
No evidence of the efficacy of oral chondroitin sulfate and glucosamine in ankle arthritis.

No evidence of the efficacy of PRP for ankle OA exists in the literature.

The efficacy of intra-articular corticosteroid injection for ankle arthritis has not been studied. In the presence of knee arthritis, meta-analysis has shown slightly longer and superior effect, compared to systemic NSAID but its long term effect was not shown.

The role of local HA injection for ankle OA (non FDA indicated use) remain highly controversial in the treatment of ankle osteoarthritis, especially compared to saline injection or exercise.
Thank you