Osteoarthritis: The Role of Injections

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DISCLOSURE

- I have no relevant financial disclosures in reference to this lecture.

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Objectives

- Osteoarthritis: What is it, and Why does it Hurt?
- Describe current injectables used in the management of osteoarthritis:
  - corticosteroids; viscosupplementation; prolotherapy; platelet rich plasma; and botulinum toxin.
- Review the current guidance for injection therapy in the management of osteoarthritis.
- Discuss the role of ultrasound guidance.
What is Osteoarthritis?
“Osteoarthritis (OA) is a DEGENERATIVE JOINT DISEASE, occurring primarily in older persons, characterized by erosion of the articular cartilage, hypertrophy of bone at the margins (i.e., osteophytes), subchondral sclerosis, and a range of biochemical and morphologic alterations of the synovial membrane and joint capsule. Pathologic changes in the late stages of OA include softening, ulceration, and focal disintegration of the articular cartilage; SYNOVIAL INFLAMMATION ALSO CAN OCCUR.”

“Despite its prevalence, the precise etiology, pathogenesis, and progression of OA remain beyond our understanding…”

Kelley's Textbook of Rheumatology
Why does Osteoarthritis Hurt?
What Causes the Pain in Osteoarthritis?

- CARTILAGE IS ANEURAL, so the joint pain must arise from other structures:
  - Subchondral bone: microfractures, medullary hypertension with bone angina
  - Osteophytes: stretching of nerve endings in the periosteum
  - Ligaments: stretch
  - Joint capsule: inflammation, distention
  - Synovium: inflammation
  - Periarticular muscle: spasm
Managing Osteoarthritis of the Knee

- GO TO therapy is strength training, NSAIDs and then a total joint replacement!
Patients don’t necessarily like Medications!

- A total of 24,081 patients were randomly assigned to the celecoxib group (mean $[\pm SD]$ daily dose, $209\pm37$ mg), the naproxen group ($852\pm103$ mg), or the ibuprofen group ($2045\pm246$ mg) for a mean treatment duration of $20.3\pm16.0$ months and a mean follow-up period of $34.1\pm13.4$ months.

- During the trial, 68.8% of the patients stopped taking the study drug, and 27.4% of the patients discontinued follow-up.

Surgery is not Benign!

- 95 patients completed the 12-month follow-up.
- The total-knee-replacement group had greater improvement in the KOOS4 score than did the nonsurgical-treatment group (32.5 vs. 16.0; adjusted mean difference, 15.8 [95% confidence interval, 10.0 to 21.5]).
- The total-knee group had a higher number of serious adverse events than the nonsurgical-treatment group (24 vs. 6, P=0.005).

Surgery may not be GO TO!

- There are an increasing number of concerns regarding the disconnect between trial evidence and orthopedic surgical practice [Lim et al. 2014].
- There are a lack of studies evaluating conservative treatments and a perceived bias towards pharmaceutical interventions [Hunter and Felson, 2006; Aspenberg, 2014; Lohmander and Roos, 2015].
- It has been suggested that a publication bias exists against reports that question established surgical procedures [Miller and Kallmes, 2010; Prasad et al. 2012].
The Injectable Lineup!
Corticosteroids
Corticosteroids

- **Rationale:**
  - Although OA is generally considered to be a degenerative, there is **evidence for low grade inflammation** to support use.

- **Products:**
  - **50 years of history** in clinical practice, there are crystalline (triamcinolone) and non-crystalline (prednisolone) forms.

- **Which Agent?**
  - There are no large, randomized, double-blind, prospective, controlled trials of various preparations with both toxicity and efficacy as endpoints. *UpToDate 2016.*

- **Efficacy?**
  - **Efficacy** of intraarticular glucocorticoids is **supported** by multiple randomized trials and meta-analyses demonstrating benefit c/w placebo and other therapies, as well as treatment guidelines from multiple professional organizations. *UpToDate 2016*
Corticosteroids: How do they Work?

- **Mechanism of Action:** complex and largely **UNKNOWN**, however, they do:
  - Reduce cytokines and inflammatory mediators;
  - Decrease capillary permeability;
  - Decline in PMN migration.

- **Treats the local inflammatory response, not the clinical problem.**

- Maximize glucocorticoid effects; minimize mineralocorticoid effects.

- Increased solubility = shorter duration = lower risk for post-injection steroid flare = lower risk for local atrophy.
Hyaluronic Acid Products
Hyaluronan Injections

- Synovial fluid is an ultrafiltrate of plasma modified by the addition of hyaluronic acid (HA), which is produced by the synovium.
- In osteoarthritis, the HA is decreased and compromised.
- Exogenous supplementation of intraarticular HA is thought to support changes in the character of synovial fluid.
Hyaluronan Products

**Mechanism of Action:**

- The **predominant mechanism** of intra-articular hyaluronan (hyaluronic acid) (HA) for the treatment of pain associated with knee osteoarthritis (OA) is **UNKNOWN**, in vivo, in vitro, and clinical studies demonstrate various physiological effects of exogenous HA.
- HA can **reduce nerve impulses** and nerve sensitivity associated with the pain of OA.
- Exogenous HA **enhances chondrocyte HA and proteoglycan synthesis**, reduces the production and activity of proinflammatory mediators and matrix metalloproteinases, and alters the behavior of immune cells.
- Many of the physiological effects of exogenous HA **may be a function of its molecular weight**.

Hyaluronic Acid Derivatives

- FDA classifies these agents as devices, not drugs.
- Indicated only for knee OA.
  - Hylan G-F20 polymers:
    - High MW preparations
    - Synvisc, Synvisc One, Orthovisc, Monovisc
    - 1-3 weekly injections
  - Sodium Hyaluronate
    - Low MW preparations
    - Hyalgan, Euflexxa
    - 3-5 weekly injections
High versus Low Molecular Weight?

- Our studies clearly demonstrate that the therapeutic effects of using HA to treat early OA may be partially dependent on downregulation of the PA/plasmin system and gelatinases expression, which delay the structural progression of the disease.

- HA with high MW MIGHT have a greater ability than that with low MW to offer effective protection for articular cartilage.

Prolotherapy
What is Prolotherapy?

- Prolotherapy is injection of an irritant solution (often a form of sugar called dextrose) into joints, ligaments, and tendons.
Mechanism of Action

- Dr. Rabago said the mechanism of action behind the prolotherapy effect is UNKNOWN but might involve "a local response which boosts the native healing reaction, possibly by an inflammatory or pain-specific mechanism."
How is it Administered?

- **Intra-articular:**
  - 10 ml syringe with 5 ml D50 and 5 ml of lidocaine 1%: 6ml injected

- **Extra-articular:**
  - Up to 22.5 ml of a 15% dextrose solution: .5 ml injections at bone tendon interfaces.

- **Recipe:**
  - 6.75 mL 50% dextrose
  - 4.5 mL 1% lidocaine
  - 11.25 mL 0.9% saline
Does Prolotherapy Work for Knee OA?

- **METHODS:** 90 adults with at least 3 months of painful knee osteoarthritis were randomized to blinded injection (dextrose prolotherapy or saline) or at-home exercise. Extra- and intra-articular *injections were done at 1, 5, and 9 weeks* with as-needed additional treatments at weeks 13 and 17.

- **RESULTS:** Adjusted for sex, age, and body mass index, WOMAC scores for patients receiving dextrose prolotherapy improved more (P < .05) at 52 weeks than did scores for patients receiving saline and exercise (score change: 15.3 ± 3.5 vs 7.6 ± 3.4, and 8.2 ± 3.3 points, respectively) and exceeded the WOMAC-based minimal clinically important difference.

- **CONCLUSIONS:** Prolotherapy resulted in *clinically meaningful sustained improvement of pain, function, and stiffness* scores for knee osteoarthritis c/w blinded saline injections and at-home exercises.

Platelet Rich Plasma
What is Platelet Rich Plasma (PRP)?
Platelet Primer I

- Platelets are formed from megakaryocytes; during its lifespan the average megakaryocyte (MK) gives rise to approximately 4,000 platelets which live an average of 9-12 days.

- The peripheral blood platelet count ranges from 150 - 450 x 10^9 /L.

- About 2/3 of platelets circulate, while 1/3 are in the splenic pool or other extravascular locations.

- In the steady state, where platelet production = platelet destruction, daily production is 30,000 - 40,000 /uL.
Platelet Primer II

- Platelets contain granules that have bioactive proteins responsible for hemostasis and healing:
  - Dense bodies contain serotonin, nucleotides (ADP) and calcium.

- Platelets release their granular contents upon activation.

- Platelets activate upon exposure to:
  - Calcium
  - Thrombin
  - Tendon derived collagen
What is PRP?

- PRP is defined as a sample of autologous blood with concentrations of platelets above baseline values.
- Clinically active PRP typically contains over 1 million platelets per microliter.
- A part of the medical frontier know as “orthobiologics.”

Why PRP?

- Platelets do more than just clot!
- Platelets release bioactive factors that:
  - Attract macrophages;
  - Attract mesenchymal stem cells;
  - Promote removal of necrotic tissue;
  - Stimulate angiogenesis;
  - Enhance tissue regeneration and healing.

- Mechanism of action in OA is largely UNKNOWN.
How do you make ‘PRP’?

1) Autologous Blood Donor

2) A PRP Preparation System is Required
   1) Differences exist in:
      1) Volume of autologous blood;
      2) Centrifuge rate/time;
      3) Activating agent;
      4) Final platelet count and growth factor concentration

3) Delivery and Activation
How long has PRP been Around?

- PRP has been safely used for over twenty years.
- Principally utilized in maxillofacial and plastic surgery.
- Additionally utilized by veterinarians.

Does PRP Work for Knee OA?

- **RESULTS:** Three meta-analyses met the eligibility criteria. All studies compared outcomes of treatment with intra-articular platelet-rich plasma (IA-PRP) versus control (intra-articular hyaluronic acid or intra-articular placebo). Use of PRP led to significant improvements in patient outcomes at 6 months after injection, and these improvements were seen starting at 2 months and were maintained for up to 12 months. It is unclear if the use of multiple PRP injections, the double-spinning technique, or activating agents leads to better outcomes.

- **CONCLUSIONS:** IA-PRP is a viable treatment for knee OA and has the potential to lead to symptomatic relief for up to 12 months. IA-PRP offers better symptomatic relief to patients with early knee degenerative changes, and its use should be considered in patients with knee OA.

Botulinum Toxin
Why Botox?

- Botulinum toxin (BT) is a neurotoxin produced by Clostridium botulinum.
- BT inhibits acetylcholine release into the synaptic cleft causing muscle paralysis.
- BT additionally suppresses neurotransmitters involved in nociceptive pain, such as Substance P and glutamate.
- The exact mechanisms of pain modulation in OA remain UNKNOWN.
Does Botox Work for Knee OA?

- **PATIENTS:** A total of 46 patients with symptomatic knee OA.
- **METHODS:** The patients were randomly assigned to 1 of the following groups: BoNT/A group (BoNT/A injection; n = 21) or control group (education only; n = 20).
- **RESULTS:** The between-group comparison revealed significant differences with regard to the pain VAS score at 1 week (P < .001) and at 6 months (P = .001) posttreatment. Similar findings for the between-group comparison were observed for the WOMAC and Lequesne indexes at 6 months (P < .05) posttreatment.
- **CONCLUSIONS:** BoNT/A provided pain relief and improved functional abilities in those with knee OA in both the short-and long-term follow-up.

What’s the Guidance… Where’s the Evidence?
Corticosteroid Injections:
- “Based on the evidence, intra-articular corticosteroids may cause a moderate improvement in pain and a small improvement in physical function, but the quality of the evidence is low and results are inconclusive.”

Viscosupplementation:
- “The analyses suggest that viscosupplements are comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events, and that HA products have more prolonged effects than IA corticosteroids. Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA.”
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<td>Duloxetine</td>
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ACR, American College of Rheumatology; NSAID, non-steroidal anti-inflammatory drug.
OARSI Guidelines: Corticosteroids

- **Recommendation:** APPROPRIATE
- **Rationale:**
  - Two recent SRs demonstrated clinically significant short-term decreases in pain. **Short-term effects were found to be significantly greater than those of intra-articular hyaluronic acid.**
  - The reviews concluded that for longer duration of pain relief, clinicians should consider other treatment options.
- **Quality assessment:**
  - Level of evidence: SR and meta-analysis of RCTs.
- **Quality of evidence:**
  - Good.

OARSI Guidelines: Hyaluronic Acid

- **Recommendation:**
  - **UNCERTAIN:** knee-only OA

- **Rationale:**
  - A recent SR demonstrated small but significant efficacy of intra-articular hyaluronic acid for knee OA pain by week 4 with a peak at week 8 (reaching moderate clinical significance) and residual benefit until 24 weeks.
  - Another review found moderate benefits of IAHA for pain and physical function in knee OA, though sensitivity analyses including larger trials or trials with adequate blinding found only small effect size for pain.
  - A third review comparing IAHA with intra-articular corticosteroids (IACS) found that while IACS provided greater benefit for pain 2 weeks after injection, IAHA provided greater benefit at 12 and 26 weeks.

- **Quality assessment:**
  - Level of evidence: SR and meta-analysis of RCTs.

- **Quality of Evidence:**
  - Good
American Academy of Orthopedic Surgeons

**RECOMMENDATION:**

- We are **unable to recommend for or against the use of intraarticular (IA) corticosteroids** for patients with symptomatic knee osteoarthritis.

- **Strength of Recommendation:** Inconclusive

- **Description:** An Inconclusive recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

- **Implications:** Practitioners should feel little constraint in following a recommendation labeled as Inconclusive, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm.

RECOMMENDATION:

- We **cannot recommend using hyaluronic acid** for patients with symptomatic osteoarthritis of the knee. Strength of Recommendation: **Strong**

- **Description**: Evidence is based on two or more “High” strength studies with consistent findings for recommending for or against the intervention. A Strong recommendation means that the quality of the supporting evidence is high. A harms analysis on this recommendation was not performed.

- **Implications**: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.
RECOMMENDATION:

- We are **unable to recommend** for or against **growth factor injections** and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee.
- **Strength of Recommendation:** Inconclusive
- **Description:** Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An Inconclusive recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.
- **Implications:** Practitioners should feel little constraint in following a recommendation labeled as Inconclusive, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.
We performed a systematic literature search for all relevant articles from 1960 to August 2014 in the MEDLINE, EMBASE and Cochrane CENTRAL.

We performed a network meta-analysis (NMA) of the relevant literature to determine if there is a benefit from HA as compared with IAS and IAP. 11 papers met the inclusion criteria from the search strategy. On NMA, those participants receiving HA were 15% and 11% more likely to respond to treatment by OMERACT-OARSI criteria than those receiving IAS or IAP, respectively (p<0.05 for both).

In the light of the aforementioned results of our NMA, the American Medical Society for Sport Medicine recommends the use of HA for the appropriate patients with knee OA.

American Medical Society of Sports Medicine

- We RECOMMEND viscosupplementation injections for Kellgren and Lawrence (KL) grade II-III knee OA in those patients above the age of 60 years of age based on HIGH quality evidence demonstrating benefit using OMERACT-OARSI Responder Rating” but the evidence should be downgraded due to indirectness for those under 60 years of age,

- “We SUGGEST viscosupplementation injections for knee OA for those under the age of 60 years of age based on MODERATE quality evidence due to response of treatment in those over 60 years of age”.

Intra-articular corticosteroids were generally recommended for hip and knee OA, although this was not universal, as the AAOS recommendation was “inconclusive”.

Intra-articular hyaluronic acid preparations were controversial, receiving recommendations (but of low strength) from OARSI, EULAR, and MQIC for hip and knee OA [17,23,24,29]; these agents were recommended not to be used by NCC-CC [21] and AAOS [18].

Intra-articular platelet-rich plasma or growth factor injections were only considered by the AAOS and evidence was found to be inconclusive to make a recommendation [18].

Summary recommendations: Intra-articular corticosteroids are recommended for knee OA; insufficient evidence currently exists to provide a general recommendation regarding intra-articular hyaluronans.

“Evidence is rather inconsistent and controversial about intra-articular (IA) injections for the management of osteoarthritis.

The most frequently used IA drugs, namely corticosteroids and hyaluronic acid products, are conditionally to fully recommended.

There are no recommendations for the use of PRP and botulinum toxin.”

Does Ultrasound Guidance Improve Outcomes?
Is Ultrasound the New Stethoscope?

Ultrasound Guided Injections: Accuracy

- Total of 99 pts with knee OA: **50 US guided and 49 palpation guided (PG) via suprapatellar bursa.**
- All had injection with HA and contrast; **USG 48/50 (96%) intra-articular, and PG 41/50 (83%).**
- **US guided intra-articular knee injections thru suprapatellar approach increases accuracy.**

Does US Needle Guidance Affect Outcomes?

- **Background and Objective:** This randomized controlled study addressed whether sonographic needle guidance affected clinical outcomes of intraarticular (IA) joint injections.

- **Methods:** 148 painful joints were randomized to IA corticosteroid injection by conventional **palpation-guided or sonographic image-guided injection.** Baseline pain, procedural pain, pain at outcome (2 weeks), and changes in pain scores were measured with a VAS scale.

- **Results:** Relative to conventional palpation guided methods, sonographic guidance resulted in **43% reduction in procedural pain** \((p > 0.001)\), **58% reduction in absolute pain scores at the 2 week outcome** \((p > 0.001)\), **62% reduction in non-responder rate.** Sonography also increased detection of effusion by **200%** and volume of aspirated fluid by **337%**.

- **Conclusions:** Sonographic guidance significantly **improved clinical outcomes.**

Improving the Quality of Care!

- **Background and Objective:** The aim of this study was to describe the one-stop approach to managing soft tissue and degenerative musculoskeletal conditions using clinic-based musculoskeletal ultrasonography (MSUS).

- **Methods:** A retrospective case record review was carried out of patients assessed and managed in the musculoskeletal clinic by a musculoskeletal and sports physician over a 10-month period.

- **Results:** A total of 1,012 patients (87%) had conditions related to the appendicular system (shoulder girdle, upper limb, pelvic girdle and lower limb) and 154 patients were referred with spinal pain. All patients with appendicular problems had a definite diagnosis and treatment initiated on the first visit to the clinic.

- **Conclusions:** The use of clinic-based MSUS enables a one-stop approach, reduces repeated hospital appointments and improves quality of care in an outpatient musculoskeletal clinic.

A Must Read!

Findings:

- **Strong** evidence that USGIs are more accurate;
- **Moderate** evidence that USGIs are more efficacious;
- **Preliminary** evidence USGIs are more cost effective.

In the Absence of Great Evidence, What Do I Do?

- **Emphasis on the Big Three:**
  - Exercise
  - Weight Loss
  - Activity Modification

- **Adjunctive Therapy**
  - CSI; Visco; PRP; Botox

- **Unacceptable Quality of Life and Failure of Non-Operative Therapy**
  - Refer for consideration of a total joint
Questions?