Regenerative Medicine:
Treatments Promoting Self-Healing

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LECOM Integrative Medicine
Primary Care Conference Peek’ n Peak
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LECOM Integrative Medicine Fellowship

• Immersive Osteopathic Experience (MD/DO)
• Medical Acupuncture
• Intro to Functional Medicine
• Nutrition & Supplement training
• ANS re-training via yoga, meditation, Heart Math and expressive writing.
• Regenerative Medicine
• Musculoskeletal Ultrasound
• Physician Self Care Focus
• Research
Lecture Intentions:

- Define Regenerative Medicine (RM) and provide clinical examples of the use with common conditions seen in musculoskeletal medicine.
- Describe how RM may decrease pharmacologic and surgical needs.
- Review specific research studies to support the understanding and use of RM.
- Discuss the role RM serves in expanding clinical options.

How do we manage chronic pain?

- NSAIDs (oral/topical)
- Antidepressants/Anticonvulsants
- Steroid Injections
- Viscosupplementation
- Narcotics
- Surgery
- Mind-Body Techniques
- Nutrition
- Manual Therapies
- Laser
- Supplements
- Medical Acupuncture
- Regenerative Medicine
What is Regenerative Medicine?

• Injections of bioactive substances into degenerative tissue with the intention of improving tissue integrity, joint function and pain.
• Prolotherapy
• Dextrose
• Autologous Blood
• Platelet Rich Plasma
• Stem Cell Therapies

Why do patients seek Regenerative Medicine?

• Looking for **options** beyond the pharmacologic and surgical approaches for their pain.
• Have an **interest** and may have read or heard about RM options helping certain pain patterns.
• RM resonates with their **belief** system to some degree. Using their own tissue to help remodel degenerative conditions.
• Motivated, able and willing to **invest** in their self-care.
Connective Tissue Insufficiency

• Chronic musculoskeletal pain is due to inadequate repair of fibrous connective tissue, resulting in ligament or tendon weakness and laxity.
• When connective tissue is weak, there is insufficient tensile strength or tightness, resulting in excessive loading of the tissues which stimulates mechanoreceptors.
• As long as connective tissue remains functionally insufficient or ineffective, these pain mechanoreceptors continue to fire with use, causing significant pain and limitation of function.
• If the laxity or tensile strength deficit is not corrected sufficiently to stop pain mechanoreceptor stimulation, chronic sprain/strain and pain result.

Regenerative Medicine

• Intentionally creating an injury ‘stimulus’ so the body can direct cellular support to the injured area.
• The initial phase of this approach is purposeful and controlled inflammation.
• Where to inject?
• When to inject?
• What to inject?
• How much to inject?
• How often to inject?
Regenerative Medicine Caveats

- Mostly 40-90 year old population seeking a nonsurgical and non-pharmacologic approach to their recalcitrant pain pattern.
- Understanding the patient's goals and are they realistic?
- Working with the anatomy they have and seeing how their body responds.
- Making them aware that this is not a panacea for all their pain.
- Typically takes 90-120 days to have tissue regeneration and reduced pain. Most patients require 3 sessions.
- If this works for one area of pain it is likely to work in others.
- 70% of patients completing our protocols can do more with less pain and reduce their medications.

Regenerative Medicine Clinical Cases

- 72 yo WM presents with bilateral sternoclavicular pain R>L.
- No change in pain pattern with 8 sessions of physical therapy or steroid burst.
- Unable to lift, play handball or even use elliptical without pain.
- X-rays wnl
- 3 treatments: starting with low density (Arthrex ACP kit) LR-PRP progressing to high density (>4 times baseline) LR-PRP 1 month apart improved pain pattern 90% and able to resume workouts within 3 months of initiating treatments.
Headaches & Inferior Nuchal Ridge Tendinosis

- 72 yo WM presents with right inferior nuchal ridge pain. S/P MRA secondary to worsening migraine pattern.
- Cervical spondylosis
- Exam c/w significant tenderness inferior nuchal ridge, supraspinous, interspinous ligament pain C2-C7
- MRA wnl
- Ultrasound revealed moderate hypoechoic tendon and cortical changes.
- 2 treatments with high density LR-PRP 1 month apart significantly reduced frequency, duration and intensity of headache patterns.

Low back pain

- 14 yo WM tennis player with 4 month history of LBP. Admits to significant growth spurt over the past 6 months.
- Completed 12 sessions of physical therapy after 2 months of being braced in neutral which improved overall pain pattern. However, doesn’t feel stable with low back.
- PE: Tenderness to palpation L4-S4 supraspinous/interspinous/sacrospinous/posterior sacroiliac ligaments. SLR [-]
- X-rays: L4/5 spondylolisthesis with grade 1 spondylolisthesis.
- Evaluated and treated at CC with epidural completed to help reduce radicular pain.
- MRI: Confirmed L4/5 pars defect and 2.3mm listhesis. No disc involvement.
- 2 sessions of low density LR-PRP combined with 15% dextrose 3 months apart has improved stability and pain. Patient returned to sport 6 months after initial treatment.
Chronic Ankle Pain

- 69 yo WM with chronic right ankle pain and swelling. Injured it years ago playing basketball. Pain limits ability to walk. Physical therapy has helped strengthen muscles around the ankle and improved balance.
- PE: Significant tenderness lateral ligament complex as well as peroneus brevis enthesis.
- X-ray: Advanced djd tibiotalar joint
- US revealed moderate ligament and stromal degeneration.
- 1 round of ABI and 3 low density LR-PRP’s over 18 months have improved functional abilities and overall pain.

Repeat Knee Arthroplasty?

- 69 yo WM presents with right knee pain. S/P 10 years ago TKR right knee with revision planned in several weeks. Patient looking for a nonsurgical approach for pain and stability.
- WOMAC- 43
- MSK ultrasound reveals moderate suprapatellar effusion with advanced degenerative changes about the medial collateral ligament as well as lateral collateral ligaments.
- PE: Significant tenderness to palpation about the soft tissue envelope right knee medial>lateral.
- Aspiration reveals synovial fluid analysis of acidic fluid with no bacteria, crystals, uric acid or autoimmune abnormalities.
- 3 sessions of 15% dextrose 6 weeks apart with alkalinizing of suprapatellar space.
- Repeat WOMAC- 4 (5 months after initial treatment)
- No suprapatellar effusion
- More stability and less pain.
Suprapatellar Effusion

- Synovial Fluid Analysis:
  - Amount/Color
  - PH
  - Uric Acid
  - Culture and Sensitivity
  - RA
  - Crystal ID
  - Lyme

Effectiveness of intra-articular injections of sodium bicarbonate and calcium gluconate in the treatment of osteoarthritis of the knee: a randomized double-blind clinical trial

Sandra Garcia-Padilla, Miguel Angel Duarte-Vázquez, Karla Elena Gonzalez-Romero, María del Carmen Camañho and Jorge L Roado

Abstract

Background: A novel therapeutic management of osteoarthritis (OA) of the knee was assessed. The study aimed to evaluate the effect of monthly sodium bicarbonate with a single (SBCG1) or double dose (SBCG2) of calcium gluconate injections on OA of the knee, as well as the efficacy and safety of both SBCG interventions in the long term.

Methods: A double-blind parallel-group clinical trial with 74 knee OA patients was performed during 12 months, both SBCG interventions were followed-up for another 6mo after intervention. The outcome variables were the Western Ontario-McMaster University Osteoarthritis Index (WOMAC), the Lequesne’s functional index and joint-space width changes from serial radiographs.

Results: After 12 months, group SBCG1 decreased −14.6 (95% CI: −14.2, −14.0) and group SBCG2 decreased −14.6 (−16.5, −12.4) in the global WOMAC score, the mean changes represent 82% and 85% lessened pain, respectively. In the Lequesne Functional Index scale, SBCG1 decreased −11.9 (−10.4, −12.4) and SBCG2 decreased −11.9 (−13.0, −10.8), representing 56 and 69% of improvement. Both mean scores were maintained after intervention discontinued. SBCG2 improved the knee’s joint space width more than SBCG1 at 3 and 18 months. Both SBCG interventions were well tolerated after 12 months of treatment.

Conclusion: A solution of sodium bicarbonate and calcium gluconate is effective in reducing the symptoms associated with OA. Its beneficial effect is maintained for one year of continuous monthly administration and at least for 6 months after the administration is discontinued. When the dose of calcium gluconate is increased, it prevents further narrowing of joint-space.


Keywords: Osteoarthritis therapy. Joint. Knee. Sodium bicarbonate and calcium gluconate.
Medial Collateral Ligament

“A joint is only as strong as its weakest ligament”

Medial and Lateral Collateral & Coronary Ligaments
Hoffa’s Fat Pad: Stem Cell Reservoir

Mayo Clinic Study:
Tensile Load, Energy Absorption & Ligament Thickness


- All these studies were performed at the Orthopedic Research Laboratory at Mayo Clinic, in conjunction with the department of neurology.
- Oh et al. demonstrated non-inflammatory (no neutrophil invasion at 1, 2, 4 or 8 weeks) collagen bundle thickening at 8 weeks in the transverse carpal ligament rabbit equivalent after a single injection of 0.05 ml of 10% dextrose into the carpal tunnel equivalent (subsynovial space) through a small incision with a 30-gauge needle.
Mayo Clinic Study: Tensile Load, Energy Absorption & Ligament Thickness

Arch Phys Med Rehab 2009;90:333-9

- This initial study was followed by three randomized, masked, two-arm studies which compared 10% dextrose versus normal saline. Single injection, Yoshii Y, Zhao C, Schmelzer JD, et al.

Mayo Clinic Study: Tensile Load, Energy Absorption & Ligament Thickness


- Yoshii Y, Zhao C, Schmelzer JD, et al. Effects of multiple injections of hypertonic dextrose in the rabbit carpal tunnel syndrome development. Hand (N Y) 2014;9:52-7. Results were evaluated successively with findings measured at 12, 12 and 16 weeks after the first dextrose injection respectively. Energy absorption and load to failure of the SSCT were measured using a standardized approach.
- The three studies demonstrated consistent and significant increases in tensile load to rupture (figure 1), total energy absorption to rupture (figure 2) and thickening of the subsynovial connective tissue. The proportional increase in ligament thickness with 1, 2 and 4 injections is seen in the figure above.
- The goal was to make an animal model of carpal tunnel syndrome by thickening the carpal tunnel ligament (transverse carpal ligament), flattening the median nerve to create carpal tunnel. The author’s hypothesis that non-inflammatory progressive transverse carpal ligament (or equivalent in animal) proliferative thickening (fibrosis) will lead to eventual median neuropathy, is supported by these studies.
- It is important to observe that there were no inflammatory cells and dextrose concentration was only 10%, confirming that this growth was not a result of inflammation but rather was a result of a proliferative effect of dextrose without inflammation.
Chondrogenic Effect of Dextrose

PMR. 2016;8(11):1072-1082

**BACKGROUND:** Dextrose injection is reported to improve knee osteoarthritis (KOA)-related clinical outcomes, but its effect on articular cartilage is unknown. A chondrogenic effect of dextrose injection has been proposed.

**OBJECTIVE:** To assess biological and clinical effects of intra-articular hypertonic dextrose injections (prolotherapy) in painful KOA.

**SETTING:** Physical medicine and day surgery practice.

**DESIGN:** Case series with blinded arthroscopic evaluation before and after treatment.

**PARTICIPANTS:** Symptomatic KOA for at least 6 months, arthroscopy-confirmed medial compartment exposed subchondral bone, and temporary pain relief with intra-articular lidocaine injection.

**INTERVENTION:** Four to 6 monthly 10-mL intra-articular injections with 12.5% dextrose.

**MAIN OUTCOME MEASURES:** Visual cartilage growth assessment of 9 standardized medial condyle zones in each of 6 participants by 3 arthroscopy readers masked to pre-/postinjection status (total 54 zones evaluated per reader); biopsy of a cartilage growth area posttreatment, evaluated using hematoxylin and eosin and Safranin-O stains, quantitative polarized light microscopy, and immunohistologic cartilage typing; self-reported knee specific quality of life using the Western Ontario McMaster University Osteoarthritis Index (WOMAC, 0-100 points).

**RESULTS:** Six participants (1 female and 5 male) with median age of 71 years, WOMAC composite score of 57.5 points, and a 9-year pain duration received a median of 6 dextrose injections and follow-up arthroscopy at 7.75 months (range 4.5-9.5 months). In 19 of 54 zone comparisons, all 3 readers agreed that the posttreatment zone showed cartilage growth compared with the pretreatment zone. Biopsy specimens showed metabolically active cartilage with variable cellular organization, fiber parallelism, and cartilage typing patterns consistent with fibro- and hyaline-like cartilage. Compared with baseline status, the median WOMAC score improved 13 points (P = .013). Self-limited soreness after methylene blue instillation was noted.

**CONCLUSIONS:** Positive clinical and chondrogenic effects were seen after prolotherapy with hypertonic dextrose injection in participants with symptomatic grade IV KOA, suggesting disease-modifying effects and the need for confirmation in controlled studies. Minimally invasive arthroscopy (single-compartment, single-portal) enabled collection of robust intra-articular data.

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Chondrogenic effect of intra-articular dextrose


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Details of Platelet Rich Plasma (PRP)

- Blood is composed of 93% RBCs, 6% Platelets, 1% WBCs and Plasma.
- The goal of PRP is to maximize the number or concentration of platelets while minimizing the number of RBCs. Generally speaking, the higher the concentration of platelets, the stronger the growth factor response.
- Platelets are naturally rich in connective tissue growth factors. Injecting these growth factors into damaged ligaments, tendons, and joints stimulates a natural repair process. But in order to benefit from these natural healing proteins, the platelets must first be concentrated.

PRP Considerations

- What areas specifically to inject?
- How many ccs to inject?
- How often to inject?
- What amount above baseline levels to deliver?
- What leukocyte concentration within the PRP? 2 spin cycle?
- Costs?
- How painful will it be?
- How much down time to expect?
Effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials


**BACKGROUND:**
Quite a few randomized controlled trials (RCTs) investigating the efficacy of platelet-rich plasma (PRP) for treatment of knee osteoarthritis (OA) have been recently published. Therefore, an updated systematic review was performed to evaluate the temporal effect of PRP on knee pain and physical function.

**METHODS:**
Pubmed, Embase, Cochrane library, and Scopus were searched for human RCTs comparing the efficacy and/or safety of PRP infiltration with other intra-articular injections. A descriptive summary and quality assessment were performed for all the studies finally included for analysis. For studies reporting outcomes concerning Western Ontario and McMaster Universities Arthritis Index (WOMAC) or adverse events, a random-effects model was used for data synthesis.

**RESULTS:**
Fourteen RCTs comprising 1423 participants were included. The control included saline placebo, HA, ozone, and corticosteroids. The follow-up ranged from 2 weeks to 12 months. Risk of bias assessment showed that 4 studies were considered as moderate risk of bias and 10 as high risk of bias. Compared with control, PRP injections significantly reduced WOMAC pain subscores at 3, 6, and 12 months follow-up (p = 0.02, 0.004, <0.001, respectively). PRP significantly improved WOMAC physical function subscores at 3, 6, and 12 months (p = 0.002, 0.01, <0.001, respectively). PRP also significantly improved total WOMAC scores at 3, 6, and 12 months (all p < 0.001); nonetheless, PRP did not significantly increased the risk of post-injection adverse events (RR, 1.40 [95% CI, 0.80 to 2.45], I² = 59%, p = 0.24).

**CONCLUSIONS:**
Intra-articular PRP injections probably are more efficacious in the treatment of knee OA in terms of pain relief and self-reported function improvement at 3, 6 and 12 months follow-up, compared with other injections, including saline placebo, HA, ozone, and corticosteroids.

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Hyaluronic Acid Versus Platelet-Rich Plasma: A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Osteoarthritis


**BACKGROUND:**
The use of platelet-rich plasma (PRP) for the treatment of osteoarthritis (OA) has demonstrated mixed clinical outcomes in randomized controlled trials when compared with hyaluronic acid (HA), an accepted nonsurgical treatment for symptomatic OA. Biological analysis of PRP has demonstrated an anti-inflammatory effect on the intra-articular environment.

**PURPOSE:**
To compare the clinical and biological effects of an intra-articular injection of PRP with those of an intra-articular injection of HA in patients with mild to moderate knee OA.

**STUDY DESIGN:**
Randomized controlled trial; Level of evidence, 1.

**METHODS:**
A total of 111 patients with symptomatic unilateral knee OA received a series of either leukocyte-poor PRP or HA injections under ultrasound guidance. Clinical data were collected before treatment and at 4 time points across a 1-year period. Synovial fluid was also collected for analysis of proinflammatory and anti-inflammatory markers before treatment and at 12 and 24 weeks after treatment. Several measures were used to assess results: (1) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale; (2) International Knee Documentation Committee (IKDC) subjective knee evaluation, visual analog scale (VAS) for pain, and Lysholm knee score; and (3) difference in intra-articular biochemical marker concentrations.

**RESULTS:**
There were 49 patients randomized to treatment with PRP and 50 randomized to treatment with HA. No difference was seen between the groups in the primary outcome measure (WOMAC pain score). In the secondary outcome measure, linear contrasts identified a significantly higher IKDC score in the PRP group compared with the HA group at 24 weeks (mean ± standard error [SE], 65.5 ± 3.8 vs 55.8 ± 3.8, respectively; P = 0.01) and at final follow-up (mean ± SE, 76.8 ± 5.3 vs 68.6 ± 3.7, respectively; P = 0.03). Linear contrasts also identified a statistically lower HA score in the PRP group versus the HA group at 24 weeks (mean ± SE, 34.6 ± 2.4 vs 48.6 ± 3.7, respectively; P = 0.001) and at final follow-up (mean ± SE, 44.6 ± 4.6 vs 57.3 ± 3.8, respectively; P = 0.003). An examination of fixed effects showed that patients with mild OA and a lower body mass index had a statistically significant improvement in outcomes. In the biochemical analysis, differences between groups approached significance for interleukin-1β (mean ± SE, 0.14 ± 0.05 pg/mL [PRP] vs 0.34 ± 0.16 pg/mL [HA]; P = 0.06) and tumor necrosis factor α (mean ± SE, 0.08 ± 0.01 pg/mL [PRP] vs 0.2 ± 0.18 pg/mL [HA]; P = 0.068) at 12-week follow-up.

**CONCLUSION:**
We found no difference between HA and PRP at any time point in the primary outcome measure: the patient-reported WOMAC pain score. Significant improvements were seen in other patient-reported outcome measures, with results favoring PRP over HA. Proceeding a significant difference in subjective outcomes favoring PRP, there was a trend toward a decrease in 2 proinflammatory cytokines, which suggest that the anti-inflammatory properties of PRP may contribute to an improvement of symptoms. Registration: ClinicalTrials.gov (Identifier: NCT02348872).

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Biomed Res Int. 2017;2017:7538604

• PURPOSE:
  • To evaluate the similarities and differences between the variety of platelet-rich plasma (PRP) formulations, preparation, and uses to try to determine the best responses for the treatment of knee osteoarthritis.

• MATERIALS AND METHODS:
  • A comparison of the outcomes of randomized controlled trials (RCTs) included in the 3 most recent and high-quality meta-analyses to classify the different studies in 2 groups (bad responders group (BRG) and very good responders group (VGRG)).

• RESULTS AND DISCUSSION:
  • From the 19 RCTs analyzed, 7 trials were included in the VGRG and 4 in the BRG. In VGRG, 1 or 2 injections were performed in 4/7 trials, time between injections was 2 to 3 weeks in 4/5 studies with many injections, volume injected varied from 2.5 to 8 mL, and single spinning technique was used in 5/7 studies. PRP classification was Mishra 4B and PAWP2Bβ in 5/7 studies. The use of PRP with leukocytes is only found in the BRG.

• CONCLUSION:
  • There is a lack of standardization in PRP preparation technique for knee osteoarthritis. However it appears that the use of a single spinning technique, a platelet concentration lower than 5 times the baseline, and avoidance of leukocytes should be preferred.

Stem Cell-Regenerative Medicine
Basic Theory: Adipose Harvesting/SVF

• The ability of adipose and bone marrow stem cells to serve as a cell reservoir for connective tissue and joint repair.

• A stem cell niche (microenvironment which favors healing) is moved from one tissue in which these niches are abundant (adipose>marrow) into one where they are scarce (a non-repairing connective tissue) pain generator.
Adipose Harvesting

Common Middle Age Realities

- Posterior horn medial meniscal tears.
- Suprapatellar knee effusions
- Reduce range of motion
- Inhibits quadriceps firing normally
- Compensatory patterns
- Inactivity
- Weight gain
- Metabolic concerns
Common Middle Age Realities

Regenerative Medicine—Dextrose—Summary Statements

Dean Reeves, MD (2019)

1. It is safe, comparable to the safety of acupuncture, as long as physicians have been fully training in needle placement methods.
2. It uses very low cost and readily available sterile dextrose solutions.
3. It is the only method of prolotherapy that can be used to treat complex cases that require treatment of many areas simultaneously for benefit.
4. Dextrose has proven ability to grow normal ligament tissue (Mayo Clinic 2008).
5. Dextrose has a unique analgesic effect that occurs in seconds without anesthetic (PM&R 2016).
6. Dextrose has been shown to stimulate some cartilage cell growth. (Before and after arthroscopy; PM&R 2016) Note, this does not resurface joints but the goal is to stabilize and calm the joint surface in arthritis.
7. Research on dextrose prolotherapy is the least affected by drug company or device company bias because there are no profit motives to publish positive results. Research is typically done by physicians sacrificing their time and personal finances. Despite that challenge, high quality trials have been published in many areas and are in process in others.
8. It appears to be effective. Other than the information offered by clinical trials, which is considerable, a general estimate is often made that 70% of patients should respond.
Regenerative Medicine Summary

• Connective Tissue Insufficiency (CTI) is ubiquitous. It’s a result of many factors including aging, injuries and nervous system upregulation. It is not a primary inflammatory issue but one of degeneration.

• Prolotherapy-Dextrose targeted for use in mild to moderate arthritic and degenerative changes.

• PRP-Prolotherapy in the form of LR-PRP for soft tissue and high density LP-PRP for intra-articular use in moderate degenerative conditions.

• Prolotherapy-Stem cell therapies appear suited for more advanced degenerative changes.

• These approaches are congruent with Osteopathic Principles and Practices.

References


References