Biologics in Sports Medicine

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• **The following presentation is free of any commercial bias

What is all this about?
• Muscles, tendons and connective tissue protect our joints and hold the various parts together.

• Once injured, tendons and ligaments do not heal easily because they naturally have poor blood supply, particularly where they connect to bone.

• As a result, the tendons and ligaments become weak and the muscles become over‐taxed causing chronic pain, weakness and further damage.

COMMON TREATMENT OPTIONS

Rest
Anti‐inflammatory medicines
Physical therapy
Bracing
Corticosteroid injections

When these treatment options are not enough or do not provide long‐term relief, Platelet Rich Plasma (PRP) therapy or other regenerative medicine treatments may be an option.
In Office Options

- PRP (Platelet Rich Plasma)
- True Stem Cell Injections
  - BMAC or BMA
  - Adipose Derived stem cells
- Amniotic Fluid/ Placental derived Injections
- Other
  - Prolotherapy
  - "Ozone" Injections/ Prolozone

In office Options

- PRP
  - Derived from Patient's own blood
  - Building evidence (Level 1 for Knee OA and Tendinopathy)
  - Most evidence here, but many questions still need clarified
  - Cost is less than other options
  - Comparison data available for Steroids/Saline/HA
In Office Options

- Stem Cell" Injections
  - BMAC or BMA Injections
    - Concept is getting true stem cell/ MSC's (also getting bone marrow derived PRP)
    - Data is nascent, but some promising (yet small, powered) studies
    - FDA ok
    - cost
    - Time will tell as data/trials come in
      - Combo treatment (slapped) or after failure of PRP?
  - Adipose derived stem cell injections
    - Theory is higher MSC's derived than BMAC/BMA
    - Very limited data
    - FDA gray area for certain products (Lipogems)
    - Some off-shore labs/ and/or FDA Trials for Cultured MSC's

In Office Options

- Amniotic Fluid/Placental Derived
  - Can be FDA gray area (typically not with Amniotic derived products)
  - Minimal data
  - No live cells...
    - There are growth factors present—application?
    - More theory than data driven practice
    - No Comparison data
    - Easy to perform
    - Cost less than BMAC/BMA

Prolotherapy

- Substance injected into joint or tendon area designed to incite inflammatory response/ theoretically creating positive pain response and healing response
- Not covered by insurance
- Typically dextrose/ lidocaine/ others
- Can have a significant inflammatory response
- Limited data regarding comparison to saline injections for knee (is saline a placebo?)
- No comparison to hyaluronic acid or PRP
“Ozone Injections”/ Prolozone

- O₃ initially used to disinfect/ currently used in municipal water treatment plants in the world
- Limited studies showing histological and biological evidence for effects of its use, certainly controversial in its use
- Theory is that O₃ inhibits inflammatory cytokines/milieu, and normalizing the cellular redox balance through the actions of cytokines
- Generated O₂ by “Ozone generator” in the office
- Administered as an injection to the affected area
- Lots of ?

PRP: History

- First promoted by M. Ferrari in 1987 autologous transfusion component after open heart operation to avoid homologous blood product transfusion
- PRP used in maxillofacial and plastic surgery since the 1990s
- Use in sports medicine has grown mostly in the last decade given potential to enhance muscle and tendon healing/ studies showing benefit of PRP for degenerative arthritis of knee
- Safety profile as well as improved development of devices for outpatient preparation and delivery/quality of MSK ultrasound have also contributed to increased use

Platelet Rich Plasma (PRP) is defined as autologous blood with a concentration of platelets above baseline values (200,000 plt/μL)

Blood typically contains 6% platelets PRP has a significantly increased supra-physiological platelet concentration.

Although this level can vary depending on the method of extraction and equipment, studies have shown that clinical benefit can be obtained if the PRP used has an increased platelet concentration of 4x greater than normal blood.
Blood contains platelets and fibrinogen, which play a crucial role in blood clotting and also carry certain growth factors that promote wound healing.

PRP is derived from your own blood, which has been processed to concentrate the platelets.

When injected into the injured site, these concentrated platelets contain powerful growth factors that can jumpstart the healing of injured tendons and ligaments by stimulating tissue repair and regeneration.

Healing/ tissue repair cascade

- **Hemostasis**
  - clot formation to degradation of platelets
- **Acute inflammatory phase**
  - Last up to 72 hours
  - Characterized by pain, swelling, redness and increased local temperature
- **Intermediate repair phase**
  - 48 hrs. to 6 weeks
  - Anatomic structures restored and tissue regeneration occurs
  - Fibroblasts, angiogenesis
- **Advanced remodeling phase**
  - 3 weeks to 12 months
  - Collagen remodeling

What are platelets? What do they do?

- **Platelets** are small discoid cells with a life span of about 7-10 days.
- Granules inside platelets contain clotting and growth factors.
- Platelets are activated and aggregate together during the healing process.
- Once activated, platelets release the granules which contain growth factors to stimulate the inflammatory cascade and healing process.
What do Growth Factors do?

- GF mediate the processes necessary for repair of soft tissues (muscle, tendon, and ligament) after acute traumatic or overuse injury
- In vitro, GF recruit reparative cells and may augment soft-tissue repair
- Animal studies have shown GF to accelerate healing, exhibit anti-inflammatory properties and stimulate cartilage matrix metabolism

**Growth Factors in PRP**

- **PDGF** (Platelet-derived growth factor): Cell growth, new generation and repair of blood vessels, collagen production
- **FGF** (Fibroblast growth factor): Tissue repair, cell growth, collagen production, hyaluronic acid production
- **EGF** (Epithelial growth factor): Promotion of epithelial cell growth, angiogenesis, promotion of wound healing
- **VEGF**: Growth and new generation of vascular endothelial cells
- **TGF-β**: Growth and neogenesis of epithelial cells and vascular endothelial cells, promotion of wound healing

**Application to Tendon Healing**

- Tendons are slow to heal and repair due to low vascularity and low energy consumption
- Growth factors can stimulate tendon repair by tenocyte activation (stimulating proliferation of tendon cells)
- Reduced scar formation/ promotion of angiogenesis/ neovascularization
Application to muscle healing

• Studies show accelerated muscle healing/quick return to sport times (in aggregate but maybe not hamstring...)
• Decrease scar formation/promotion of blood flow

Application to bone/degenerative conditions

• Promising results when compared to hyaluronic acid and steroid injections for knee degenerative arthritis regarding length of pain relief/return to function/functional outcome—especially for earlier stages of arthritis
• Possible benefit for cartilage defects/fractures/various MSK disorders
• Much detail and information yet to be established—regarding standard protocols, much variability in individual platelet counts/concentration systems. More studies are needed to define these questions

PRP: how is it performed?

• A small sample of blood is taken from the patient (30-60 cc)
• This sample is then placed into a centrifuge.

• The centrifuge separates the sample into
  • red blood cells
  • the buffy coat/platelet rich plasma
  • platelet poor plasma
PRP: how is it performed

• This platelet rich plasma is then injected into the targeted tissue (joint/tendon/muscle etc) preferably under MSK ultrasound visualization and guidance.
• Responses to treatment vary, but most patients will need one to three injections.

• Each set of treatments may be spaced approximately one to four weeks apart.

PRP therapy may eliminate the need for more aggressive treatments such as invasive surgery or long-term medication.

PRP therapy is not a quick fix.

The therapy stimulates the growth and repair of tendons and ligaments, which requires time and rehabilitation.

My experience

• Started doing PRP under MSK US guidance in 2012

• Over 1500 PRP injections done to date

• 2 studies approved by BayCare IRB ongoing in process (Proximal Hamstring Tendon and Plantar Fascia) Plus Case report involving competitive pediatric gymnasts with recalcitrant lateral epicondylitis (X 1 year+ each)

• Tactical Precision is key: MSK US

• Some protocols are being better refined: knee degenerative arthritis—series of bihorns—

• Interesting results of combined PRP + HA: could this become new treatment protocol?

• Many patients referred by prior patients whom have had PRP in the last 4 years and very happy with functional improvement and outcome

• Have treated physicians, athletes, “weekend warriors”, and various people who could not afford to continue to have activity curtailed by their MSK problem

My Experience:

• Clinical Journal of Sport Medicine:
  • March 2017 - Volume 27 - Issue 2 - p 193-230
  • doi: 10.1097/JSM.0000000000000417
  • Abstracts

• Treatment of Plantar Fascial Tendinosis With Ultrasound Guided Platelet-Rich Plasma Injection
  • Michelle Hummel, BS, Kevin Elder, MD, and James Vogler, MD
PRP: evidence is growing for treatment of knee degenerative arthritis and tendinopathy

- THE PHYSICIAN AND SPORTSMEDECINE, 2017
- The Effectiveness of Platelet-Rich Plasma in the Treatment of Tendinopathy.

**Conclusion:** There is good evidence to support the use of a single injection of LR-PRP under ultrasound guidance in tendinopathy. Both the preparation and intratendinous injection technique of PRP appear to be of great clinical significance.
Early Knee OA

• Studies directly comparing PRP to hyaluronic acid show superior pain/functional outcome with PRP as well as improved symptom scores for longer periods of time.
• Generally patients that did better were younger patients with earlier stages of knee arthritis.
• Some recent studies showing better effects with doing series of injections (3) rather than single injection for knee arthritis.

What does the Data Say?

• Growing body of evidence, especially in regards to knee OA.
  • In the past 5 years, 11 directly comparing PRP to intra-articular hyaluronic acid injections showed better symptom scores and clinical outcomes at 12 months post-treatment in PRP groups.
  • Tendinopathies:
    • Lateral/medial epicondylitis
    • Plantar fasciitis
    • Achilles tendinopathy
    • Rotator cuff
    • DeQuervain's TS
    • Hamstring/Quadriceps/Gastrocnemius
    • Gluteus tendinopathy
  • Other:
    • Hip arthritis
    • Arthritis degenerative meniscus (not mechanically locking)
    • Peripheral neuralgia/CES
    • Discogenic back pain.

Absolute Contraindications

• Platelet dysfunction syndrome
• Critical thrombocytopenia
• Hemodynamic instability
• Septicemia
• Local infection at the site of the procedure
• Patient unwilling to accept risks
Relative contraindications

- Consistent use of NSAIDs within 48 hours of procedure
- Corticosteroid injection at treatment site within 1 month
- Systemic use of corticosteroids within 2 weeks
- Tobacco use
- Recent fever or illness
- Cancer—especially hematopoietic or of bone
- HGB < 10 g/dl
- Platelet count < 105/μl

Limitations of PRP

- Lack of standardization in the preparation of PRP (Several companies with competing products)
- No standardized number of injections, timing or known optimal volume of injection
- Many published studies have small sample numbers—sometimes without controls
- Not known whether white cells should be included or not? If included: what type of white cells?
- Important to recognize when need for surgical involvement

Cost

- Many insurers are still slow to cover but...
  - Some patients have FSAs etc and submit to have covered
  - Some insurances sometimes cover with supporting info/notes which can be provided
  - What is cost to health of lost activity level for chronic non healing injury?
  - What is cost to health of chronic NSAIDs?
  - Some surgical treatments for chronic tendinopathy do not have great outcomes...and patients often want to avoid surgery in the first place
True “Stem cell” Injections: BMAC

- Bone marrow aspirate taken from patient- several locations possible, often taken from hip/posterior iliac crest
- Local anesthesia used to numb up area for bone marrow aspirate which is done in office/ or O.R.
- Bone marrow aspirate placed into a centrifuge which then separates the sample
- A sample containing the stem cells is then injected into the targeted tissue/joint
BMAC

- Patient given mild anxiolytic to help stay calm during procedure
- Otherwise only local anesthesia used (Ropivicaine to numb skin/subcutaneous tissue and periosteum while taking sample)
- Hand driven Jamshidi needle
- Area of posterior iliac crest identified using MSK ultrasound
- Procedures/injection of bone marrow aspirate concentrate (BMAC) performed using MSK ultrasound guidance
- Total time in office approximately 2 hours
BMAC: Theory versus reality

- Because there are higher concentrations of growth factors/true stem cells, it is thought that the treatment should be more potent/have greater effect than PRP itself.
- There are studies showing very positive effects on actual cartilage regrowth, etc. but most of them are animal studies.
- There are a few human studies so far published.
- Despite the lack of data, there is a growing interest in developing protocols involving BMAC.
  - Knee DJD: BMAC followed by PRP 4-6 weeks later.
- Isolated case reports of meniscus regrowth followed by MRI— as well as osteochondral/cartilage defects resolved by treatment with BMAC injections generate excitement and hope— however data is nascent, lack of trials not affected by bias/etc.

Knee OA Pre-BMAC:
February 2018 May 2018
Is BMAC just expensive PRP?

- Cassano KSSTA 2016
- Bone marrow concentrate and platelet-rich plasma differ in cell distribution and interleukin-1 receptor antagonist protein concentration.
- 29 patients: PRP vs BMA: BMAC
- Bone marrow-derived samples were cultured to measure colony-forming units, and flow cytometry was performed to assess mesenchymal stem cell (MSC) markers.
- Cytokines and growth factors important for cartilage repair were measured using multiplex ELISA.
- Colony-forming units were increased in both BMAC compared to BMA (p < 0.0001).
- TGF-VEGF higher in BMAC than PRP (p<0.024, p<0.0001).
- IL-1ra concentrations were greater (p = 0.0018) in BMAC samples (13,432 pg/ml) than in PRP (588 pg/ml).

What is this IL-1ra

- Orthokine
- IRAP
- Regenokine

Adipose Derived Stem Cell products also exist

- Thought to generate a higher number of cells than BMAC
- Requires more tissue manipulation/Processing than BMAC
Adipose-Derived Stem Cells

- Must meet FDA criteria for minimal manipulation of cells performed same day.
- There are few choices in this regard
- Lipogems:
  - Closed loop device for autologous adipose tissue
  - No centrifuge required
  - Progressively micro-fractures adipose tissue clusters minimizes inflammatory oily and blood residue
  - No enzymatic digestion
  - Produces injectable version of structural adipose tissue/can be injected with 22-gauge needle

Adipose derived stem cells

- Evidence historically has lagged way behind BMAC—BMAC has the longest and greatest evidence of efficacy for orthopedic conditions
- More recent studies comparing directly to BMAC showing some equivalent benefit
- Safety appears to be very good with similar contraindications as seen with BMAC
- Same concerns re: low N studies/bias/ lack of control/ observational etc

Stem cell injections: BMAC and adipose derived

- Cost is generally 6-10 times that of PRP
- More time consuming and technically involved
- No insurance coverage
- Generally reserved for challenging cases where there may not be other options or patient has already failed other available options
- Is there a sweet spot for BMAC?
- Effect of significant higher growth factors?
- As with PRP, safety profile from this autologous product appears to be excellent
- Data is nascent, but recent studies showing lasting functional relief >1 year, possible delayed progression to joint replacement
Amniotic Fluid derivatives

- Several companies now producing products
- No live cells (dehydrated membrane grafts). Getting growth factors
- These are not "stem cell injections"
- Minimal data:
  - The role of dehydrated human amnion/chorion membrane allograft injection (dHACM) for the treatment of tendinopathy or arthritis: a case series involving 40 patients
  - Alfred C. Gellhorn, Alex Han
  - PM & R: the Journal of Injury, Function, and Rehabilitation 2017 May
- Easy to perform (material comes ready to draw up and inject)
- Cost more than PRP/ less than BMAC/BMA
- Time will tell/ ? Adjunctive treatment?

48-year-old patient without other significant medical history presents to you with history of 2 months of progressive knee pain, x-rays reveal mild arthritis, no fractures. He describes some pain at the medial joint line with increased activity levels, no locking or catching of the knee, occasionally his knee will swell. Reasonable options for him as treatment would include:

1. Aggressive early arthroscopy to "clean out" the knee.
2. Encourage patient to invest in 20 sessions Cryo immersion therapy because it is proven to help knee pain.
3. Symptomatic treatment, ice and anti-inflammatories broadly. Consider single steroid injection if clinically appropriate/desired. If activity limitation is not resolving condition can offer biologic treatment such as PRP.
4. Medrol Dosepak followed by chelation therapy and coffee enemas QID.

Which of the following are examples of stem cell treatment as defined by the FDA?

1. Platelet Rich Plasma (PRP)
2. Bone Marrow Aspirate Concentrate (BMAC)
3. Placental matrix/ amniotic derivatives
4. PRP therapy
5. Adipose derived stem cells
6. REO Speedwagon
Current theory on the mechanism of action of PRP in resolving knee pain is:

1. Cell induced “curing” of arthritis.
2. Platelet rich plasma stays in joint and creates lubrication and cushion.
3. Growth factor release from platelet rich plasma activation induces various paracrine signaling processes within the knee down regulating inflammatory processes, creating natural production of hyaluronic acid and general induction of more anabolic state.
4. Inagaddadavida baby.

Summary/Pearls

- PRP is an excellent option to consider for lasting functional improvement and pain relief for patients with chronic tendinopathy injuries and/or DJD. The data for PRP has grown significantly in the last 5 years. More research is needed to continue to refine the process.
- BMAC is an exciting concept that may have important significance. Data is very nascent regarding this application but growing. There may be patients that this is the perfect treatment for or those whom have exhausted all other options. Is it better for certain joints/areas than others?
- Amniotic Fluid derivatives are available, these are easy to administer, “prepackaged” do not require extraction, but have limited data regarding efficacy.
- These treatments should be done with consideration to exploring the whole kinetic chain/ referral to physical therapy to correct any contributing deficits.
- Not for everyone: there are contraindications.
- Some patients may have need for surgery (ie: complete ACL tear/ severe DJD/etc.) Each case is considered individually.
- XR and diagnostic US done in office, other studies ordered as needed.
References


Thank You!!!