

The Wild West – Stem Cell: From the Athlete to the Weekend Warrior

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Overview

- IOC consensus paper on the use of PRP in sports medicine
 - Engebretsen et al. Br J Sports Med 2010
 - “Work in Progress, need more studies, indications and outcomes better understood”
- The number of STEM cell clinics has roughly doubled every year since 2010

Father of Sports Medicine

- Galen 100AD
 - “Athletes over indulge, live shorter and get arthritis”

Regenerative Medicine for Cartilage in the Athlete

- **The problem**
- Managing expectations
 - All regenerative medicine is not created equal
- What can we treat
- Outcomes
- Next Steps

Cartilage Injury

- ACL tears
 - Up to 50% of athletes that undergo ACL reconstruction have cartilage damage
 - 200,000 ACL injuries per year = ~100,000 cartilage lesions just from ACL injuries

Articular Cartilage Injury Mechanisms

- **Acute Injury: ACL**
 - Catabolic “Bone Bruise”
 - ↓ GAG Content (chronic)
 - ↓ Aggrecan Levels after 2 yrs
 - Chondrocyte Apoptosis
 - Traumatic Focal OC Defect
 - Incidence 9-60%
 - Shear Injury/Compression
 - Forces > 25-35 MPa
 - Subchondral Bone Fracture

Chondroprotection and Chondrofacilitation

- **Hyaluronic Acid Injection**
- **Cytokine Modulation**
 - IL-1ra - Inhibition of Inflammatory Response
- **PRP**
- **Growth Factor Augmentation**
 - Factors: BMP-7, BMP-4, FGF-18, IGF-1
 - Stimulation of: MSC-Differentiation, Proliferation, Metabolism
- **Stem Cells**
 - Adipose derived
 - BMAC

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STEM cell Expectations...Need to know basis

- What and why is effective?
- For what and when?
- Which do we use?
- How much?
 - Dose / volume of treatment?
 - Number of injections
 - Treatment Intervals
- Need Platelet activation?
- Treatment protocol
 - When to treat?
 - Adjuvants HA, ADSCs/BMAC
 - Rehab, exercise, RTS?

Hyaluronic Acid

- Safety has been documented: over 675 published studies
- Efficacy has been demonstrated: **28 RCTs/ 3 meta analyses**
- Questions still persist about associated chondroprotective effect in humans
- Short-term efficacy

What Does it Treat?

- Regenerative medicine has been used to treat a variety of injuries and conditions:
 - Tendon injuries
 - Achilles tendonitis, rotator-cuff injuries and “tennis elbow.”
 - Arthritis and cartilage injuries.
 - Plantar fasciitis
 - Muscle strains.
 - Ligament sprains.
 - Degenerative disc disease.
 - Facet joint arthritis.

Biologic Therapy Contraindications

- Acute systemic infection
- Local infection at or near site
- Malignancy (remission), with the exception of nonmetastasizing skin tumors such as squamous cell carcinoma or basal cell carcinoma
- PRP therapy is not recommended in thrombocytopenia or those who use nonsteroidal anti-inflammatories in the two weeks
- Pregnancy

Autologous Interleukin-1 receptor antagonist improvements RCT in OA

- Will I get what Kobe got?
 - Regenokine

	Platelets (growth factors)	WBC (catabolic cytokines)	Stem Cells
PRP	+++	+	+
ACS / IRAP	+	+++	--

- Theory: blood is removed weeks before and incubated with borosilicate (CrSO_4) coated glass beads with stimulates IL-1ra
- Likely not as effective as PRP.
- Cost: \$1,000 to \$2,000

Platelet Rich Plasma

- Growth factors released from platelet α -granules
 - Enhances release of NF-kappa-beta inhibitor, and thus reduce NF-kappa-beta signaling and dampen its downstream inflammatory cytokine activation
 - (TGF, PDGF, VEGF, BMPs, *IGF-I*)
 - **Some is good**  **more is better**
- **Cost: \$500 - \$2,000**

Not All PRPs are Created Equal

- Platelets, WBCs, RBC reduction, and Platelet:WBC vary widely in the different commercially available products
- Leukocyte-rich vs leukocyte poor

More Than Just Platelets

Bone Marrow Aspirate Concentrate - BMAC

- Bone Marrow contains a high concentration of "pluripotent" stem cells that can be withdrawn from the hip bone
- The theory: "undifferentiated" cell will replicate in to various types of tissues that could heal injuries
- Where's the Matrix?
- Cost: \$2,000 - \$5,000

Mesenchymal Stem Cell (MSC) from Bone Marrow

- Rare, undifferentiated multipotent stem cell
 - Relatively mature
 - Less capacity for differentiation
 - Must differentiate in to fat, bone, and cartilage
 - Can differentiate in to muscle, tendon, and ligament
 - MSC receive local paracrine signals
 - Leads to proliferation and differentiation to surrounding host tissue
 - Immunosuppressive
 - 0.01 to 0.001% of nucleated marrow cells
 - Declines with age

Adipose Derived Concentrate _ ADC

- Harvested from adipose tissue
- Very powerful cells
 - Many different pathways
- Need a scaffold
- Cost: \$2,000 - \$15,000

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Tendon Injury - PRP

- "The evidence for all primary outcomes was judged as being of very low quality."
 - Methods for preparing and quantifying PRP therapies lack standardization.
 - Evidence to support the use of PRP therapies for treating muscle and tendon injuries is lacking, both overall and for specific conditions.
- Common problems with research
 - Small number of participants
 - Blinding of participants and/or outcome assessors not performed or not described
 - Treatment preparation not standardized among trials

Tendon Injury – STEM cell

- Current evidence is limited and unconvincing
 - Low patient numbers
 - Small number of trials using expanded MSCs
 - Little to no control groups
 - High risk of bias

Muscle Injury

- Few randomized trials
 - High risk of bias
- No statistical significant difference in reinjury rates with PRP
- STEM cell treatment – limited research

Osteoarthritis

- Luekocyte poor superior to leukocyte rich
- High degree of bias in studies
 - Studies were favorable for both PRP and STEM cells
- Not many good control trials

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Patients with Early OA did better

Early OA – HA vs PRP

- **Patients treated with PRP showed better results at 1-year follow-up than patients treated with hyaluronic acid; the results deteriorated over 12 to 24 months of follow-up**

Anecdotal – it works

- That said, there is a high placebo effect
- Get what you pay for
- More willing to be compliant with rehab/restrictions

Next Steps

- Three Food and Drug Administration scientists in the *New England Journal of Medicine* looking at the benefits and risks of this kind of stem cell therapy, “This lack of evidence is worrisome.”



Case Western Reserve / University Hospitals

Sports Medicine Institute

FDA Approved Stem Cell Study

Collaboration: UH Sports Medicine and NCRM

- FDA IND approved
- Pilot study: Intra-articular autogenous, expanded MSC injections (50 x 10⁶ MSCs) in 20 patients age 18-60 y.o. with:
 - Early knee OA
 - Focal cartilage defects.
- Stem cell expansion performed by the Cellular Therapy Integrated Services (CTIS) of the NCRM
- Followed 2 years, functional outcomes, pain scale, MRI, synovial fluid analysis.
- **Does increased concentration of stem cells improve outcome?**

Thank You

- Questions