Regenerative Medicine
Changing the Game in Orthopedics

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OBJECTIVES

- Understand the basic principles behind the science of treatments with platelet-rich plasma and bone marrow concentrate injections for various orthopedic problems
- Learn about current research regarding treatment with stem cells in orthopedics
- Understand which patients would be ideal candidates for treatment
Teaching consultant for Arthrex
SPOILER ALERT!

- Basic science and in vitro studies for PRP and BMC demonstrate the release of growth factors and their potential role in healing.
- Robust trials and in vivo studies are scarce and sometimes have conflicting results.
- Lack of strong clinical evidence is due to the wide variety of PRP/BMC preparations, extractions, cell counts, growth factor yields or activity, lack of post-procedure protocols.
- Differences in tissue types, injuries and patient comorbidities also contribute to the broad range of study results.
- Despite all of this, there continues to be extensive utilization of these products.
THE PROBLEM

- 45 year old active male with moderate osteoarthritis of his knees
- Continued pain despite:
  + Weight loss
  + Home Exercises /Physical Therapy
  + Activity modification
  + NSAIDs / Glucosamine /Chondroitin
  + Cortisone Injection
  + Viscosupplementation
  + Unloader Brace
  + Prior arthroscopic debridement with microfracture
CASE 1

- Too young to replace the knee

What can you do for him?
THE PROBLEM:

- Anti-inflammatory Medications
- Glucosamine/Chondroitin
- Cortisone Injection
- Viscosupplementation
- Steroids

These focus on relief of symptoms, rather than improving the biochemical environment and/or structure of joints.
What if he could significantly delay or even prevent progression to this...
WHAT IS REGENERATIVE MEDICINE?

Scientific field that focuses on new approaches to the process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function.

- Utilize your body’s stem cells and blood platelets for healing and repair
  - Bone marrow concentrate injections
  - Platelet Rich Plasma injections
WHEN DO WE USE REGENERATIVE MEDICINE?

- Patients coping with arthritis, sports injuries, tendon strains, sprained ligaments, muscle injuries and more
- Faster healing as well as improved functionality both are possible with innovative, cutting-edge adult stem cell and PRP procedures.
WHAT HAS BENEFITED FROM THESE PROCEDURES?

- Osteoarthritis
- Meniscus tears
- Chronic tendinitis/tendinosis
- Labral tears of the hip or shoulder
- Partial rotator cuff tears
- Tennis elbow
- Plantar Fasciitis
- Trochanteric Bursitis/Gluteus Medius Tendinopathy
- Sacroiliac (SI) Joint Dysfunction
- Degenerative Disc Disease
- Avascular necrosis
THOUGHTS ON STEM CELLS?
WHAT ARE STEM CELLS?

- Undifferentiated "immature" cells
- Found throughout your body
What is a Stem Cell?
A mesenchymal stem cell is a primitive cell with the ability to:

- Reduce Inflammation
- Self Replicate
- Fight Apoptosis (Cell Death)
- Differentiate into Multiple Tissues: Muscle, Bone, Fat, Cartilage
STEM CELLS

Prenatal (embryonic) $\times$ Stem Cells
Postnatal (adult)
POSTNATAL (ADULT) STEM CELLS

- More readily available
- Less political / ethical ramifications
- Multiple sites are available for isolation of adult stem cells, including:
  - adipose
  - peripheral blood
  - periosteum
  - synovium
  - bone marrow
  - skeletal muscle
  - umbilical cord
  - dental pulp.
STEM CELLS

Stem Cells

Prenatal (embryonic)

Postnatal (adult)

Mesenchymal Stem Cells (MSCs)
MESENCHYMAL STEM CELLS (MSCS)

- Stem Cells of interest in orthopedics
  - 1. Capacity for transformation into bone, fat and cartilage cells (help to regrow cartilage)
  - 2. Induce production of specific “T helper cells” which produces an anti-inflammatory state
    - Decreased interferon gamma (inflammatory)
    - Increased Interleukin 4 (anti-inflammatory)
  - Capacity for self-replication
  - Immunomodulatory properties?
MSCS HOMING TO INJURY SITE

Damaged Cartilage

MSCs
STEM CELLS

Prenatal (embryonic)  Mesenchymal Stem Cells (MSCs)

Postnatal (adult)  Bone Marrow  Adipose tissue
BONE MARROW INJECTIONS

- Most abundant source of MSCs
- Most studied in literature and first available for use
- Obtained through simple bone marrow aspiration
- Good for treating multiple orthopedic problems for a potent effect
BONE MARROW ASPIRATION

Cortical bone

Spongy bone

Marrow

Pelvis
BONE MARROW CONCENTRATE

- Contains mesenchymal stem cells (MSCs), hematopoietic stem cells, platelets (containing growth factors), and cytokines
- Anti-inflammatory and immunomodulatory properties can facilitate regeneration of tissue
- Available for a same-day procedure with minimal manipulation of cells
- Compliant with FDA restrictions
- Several publications report ease of use, strong safety profile

BONE MARROW CONCENTRATE
Why Concentrate Bone Marrow?

BMA at 96 hrs

Angel BMC at 96 hrs

Healing trinity: **Cell**, **Signal**, **Scaffold**
## Technology Changes Everything

<table>
<thead>
<tr>
<th>Arthrex Angel BMC</th>
<th>Platelet Concentration (K/μL)</th>
<th>Nucleated Cell Concentration (K/μL)</th>
<th>Hematopoietic Cell Concentration (K/μL)</th>
<th>Total Neutrophil (x10^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMA</td>
<td>87.7 ± 6.4</td>
<td>24.5 ± 15.6</td>
<td>0.002 ± 0.001</td>
<td>612.1</td>
</tr>
<tr>
<td>BMC</td>
<td>787.0 ± 317.6</td>
<td>240.5 ± 186.6</td>
<td>0.081 ± 0.056</td>
<td>132.9</td>
</tr>
<tr>
<td>Increase Above Baseline</td>
<td>-9x</td>
<td>-10x</td>
<td>-33x</td>
<td>↓80%</td>
</tr>
</tbody>
</table>

>80% recovery of the hematopoietic cell lines with an 80% reduction in the undesirable neutrophil cell content.

![Bone Marrow Aspirate](image1)

![Angel BMC](image2)
ADIPOSE AS STEM CELL SOURCE

- Obtain from “love handles”
- No culturing
- Claims of 1000x stem cell concentration as bone marrow
  - Does not have as many mesenchymal stem cells as bone marrow
- Over 1700 peer reviewed papers published
- Use as a scaffolding for bone marrow stem cells
LIPOASPIRATE

Aspirate the adipose tissue.

1. Aspiration
2. Centrifugation
3. Injection
Ultrasound guidance is utilized for targeted placement of the injection of fat tissue and bone marrow concentrate.
PRP/BMC AND LIPOADSPIRATES

- The combination of fat with PRP (or BMC) has been reported to enhance the tissue acceptance of autologous grafts in thousands of cases in the aesthetic literature.
- Numerous conditions can benefit from this grafting technique, including tendinoses, partial to full thickness tendon tears, interstitial tendon tears, ligament tears, muscle strains/fibrosis, osteoarthritis, and disc damage.


ARTICULAR CARTILAGE

- Limited ability to self-repair after injury
- Current methods to treat:
  - Bone Marrow stimulation (microfracture)
  - Osteochondral autograft transfer
  - Osteochondral allograft
  - Autologous chondrocyte implantation (ACI)
Nejadnik, et al compared treatment of knee cartilage defects with bone marrow-derived stem cells (BMSCs) and autologous chondrocyte implantation (ACI)

- Improvement in patient’s quality of life in both groups
- No significant difference between BMSC and ACI group in terms of clinical outcomes except for physical role functioning, with greater improvement in BMSC group.
- BMSC group is less invasive, normal articular cartilage is not damaged, one less surgery, less cost

Kim et al performed BMC injections (with adipose tissue) in 41 patients (75 knees) with OA of the knee.

They found significant improvement in pain and function in patients with KL Stage 1 – 3 arthritis.
Oliver et al evaluated clinical efficacy of autologous intra-articular BMC and lipoaspirate as treatment option for the knee.

Evaluated treatment for 70 patients diagnosed with Kellgren-Lawrence Stage 2-4 Knee OA at 90 and 180 days.

Function and Symptoms monitored through Knee Injury and Osteoarthritis Outcome Score (KOOS).

- Found significant improvements in Pain, ADLs, Symptoms, Quality of Life and Sports/Recreational activity.

Concentrated Bone Marrow Aspirate for the Treatment of Chondral Injuries and Osteoarthritis of the Knee

A Systematic Review of Outcomes

Jorge Chahla,* MD, Chase S. Dean,* MD, Gilbert Moatshe,*† MD, Cecilia Pascual-Garrido,‡ MD, Raphael Serra Cruz,*§ MD, and Robert F. LaPrade,*¶ MD, PhD

Investigation performed at Steadman Philippon Research Institute, Vail, Colorado, USA

Systematic Review, 11 studies
- 5 prospective, 1 retrospective, 2 case series, 3 case reports
- Main finding of this review was good to excellent overall outcomes reported with the use of BMAC for the treatment of early knee OA and moderate chondral defects
- Level of evidence varied from 2 to 4
CARTILAGE REGENERATION?

- Documented case reports of increased cartilage and meniscus volume on MRI.

Fig. 1. Pre-injection. Left shows cartilage and right shows meniscus.

Fig. 2. Six months post-injection. Left shows cartilage and right shows meniscus.
REFRACTORY TENNIS ELBOW

- Already demonstrated efficacy with PRP (51 pts) over cortisone injections (49 pts) at 2 year follow up (double blind, placebo controlled study)

- BMC treatment has shown significant improvements in pain and function in short to medium term follow-up
BMC used as an adjunctive therapy during rotator cuff repair enhanced the healing rate and improved quality of the repaired surface.

- **BMC treated**
  - 45/45 (100%) treated healed by 6 months
  - 39/45 (87%) had intact rotator cuff at 10 years

- **Non-BMC treated**
  - 30/45 (67%) healed by 6 months
  - 20/45 (44%) had intact rotator cuff at 10 years

Hernigou P et al. Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: a case-controlled study. International Orthopaedics. 2014. 38: 1811-1818
SUPRASPINATUS TENDINOPATHY

Supraspinatus
Defect
Humeral Head
SUPRASPINATUS TENDINOPATHY
OTHER AREAS OF BENEFIT

- BMA Treatment of nonunion fractures
  + 82% (9/11) had healing after 6 months
  + Improvement in pain and function

- Lumbar Discogenic Pain
  + 80% (21/26) had significant reductions in pain and impairment through 12 months
  + 40% (8/20) were noted to have rehydration of treated discs on MRI
OTHER AREAS OF BENEFIT

- Avascular necrosis
  + Retrospective review over 13 years
  + 594 hips treated with core decompression combined with bone marrow concentrate
  + Significant improvements in pain and function of treated patients
  + Only 17% progressed to hip replacement (40% with core decompression alone)

PLATELET-RICH PLASMA
The concept of PRP is using your own platelets and growth factors to heal the injured site.
- transforming growth factor, insulin-like growth factor, fibroblast growth factor, and platelet-derived growth factor.
- We take a sample of your blood and place it in a centrifuge to obtain a concentrated sample of growth factors—can be 5 to 10 times greater than usual.
- Platelet is activated upon injection
- Releases growth factors
- Increases anabolic signaling
PROCEDURE FOR PRP

1. Collect 30-90ml of blood
2. Centrifuge
3. Collect 3-7ml PRP
4. Inject to specific site
DOES PRP WORK?

**Significant Difference**
- Peerbooms, AJSM, 2010
- Kon, KSSTA, 2010
- Filardo, KSSTA, 2010
- Radice, Arthroscopy, 2010
- Wang-Saegusa, AOTS, 2011
- Thananas, AJSM, 2011
- Gosens, AJSM, 2011

**No Difference**
- Silva, KSSTA, 2009
- De Vos, JAMA, 2010
- Vogrin, ESR, 2010
- Creaney, BJSM, 2011
- DeJonge, AJSM, 2011
- Schepull, AJSM, 2011

PubMed article search: 8,200
NOT ALL PRP CREATED EQUAL:

Medium platelet numbers
Full leukocytes
Erythrocytes

Concentrated platelet numbers
Varying leukocyte composition
Varying erythrocytes
Custom PRP concentrations

Low platelets
Low leukocytes
Erythrocytes

Low platelets
No leukocytes
No erythrocytes
PRP RE-FORMULATED PER INDICATION

- PRP
  + Platelets
  + Growth factors
  + WBCs
  + RBCs

- Uses:
  + Tendinopathy
  + Ligament and Tendon healing
  + OA
**ROLE OF LEUKOCYTES**

- In contrast to platelets, leukocytes contain and produce cytokines that are catabolically active and promote inflammation.
- Promote chemotaxis, proliferation and differentiation of cells.
- Induce extracellular matrix production and angiogenesis.
- Release inflammatory cytokines: IL-1β, IL-6, INF-gamma, TNF-α.
- Reactive oxygen species.
LP VS LR-PRP

- LP-PRP has been shown in numerous studies to be ANTI-inflammatory
  - Increased IL-4, IL-10

- LR-PRP is PRO-inflammatory
  - Increased IL-1Beta, IL-6, IFNGamma, TNF-Alphas
The efficacy of PRP treatment improves with tailored formulations for specific conditions:

- Tendinopathy: LR-PRP
- OA: LP-PRP
- Muscle Injury: PPP?

MSCS AND PRP

- It has been demonstrated that by combining PRP and MSCs in vitro a 10-fold increase stem cell activity

- Haynesworth et al showed that human mesenchymal stem cell proliferation is proportional to the platelet concentrations in PRP, and it begins at a 4- to 5-fold increase in platelet numbers
  - Haynesworth SE, Kadiyala S, Liang LN: Mitogenic stimulation of human mesenchymal stem cells by platelet release suggest a mechanism for enhancement of bone repair by platelet concentrates. Presented at the 48th Meeting of the Orthopaedic Research Society, 2002, Boston, MA

- Future studies needed in this area
Consult will assess if patient is a candidate for Stem Cell/ PRP.

We ask to bring any imaging. MRI not always necessary.

Sometimes we may have to stop certain medications for 2-3 weeks prior to procedure and for 6 weeks after procedure.

- Steroids, NSAIDS, Aspirin, Statins and ACE inhibitors
Patients who are not candidates:

- Patients with blood borne cancers (lymphoma or leukemia) or other malignancies
- Patient with any current infection
- Patients on high dose blood thinners
- Patients with multiple medical issues may not be good candidates
WHAT DETERMINES HOW A PATIENT WILL RESPOND TO TREATMENT?

1. Severity of the problem?
2. “Healing potential” of the patient
   - Age, medical problems, medications, social history, etc.
3. Physician treatment
   - Product used, collection of PRP/BMC, machine used to process, formulation (cell content), separation into syringes, placement of injection(s)
4. After Treatment?
The total procedure time takes approximately 60-90 minutes, including preparation, treatment and recovery time. **Performed in the medical office without general anesthesia** or hospital stays, and without a prolonged recovery period.

Most patients have increased pain for 3-5 days after the procedure.

Most patients return to their jobs or usual activities within a couple of days.
The healing and repair usually takes 2-3 months but improvement is usually noted before that time.

Follow up appt 4-6 weeks after the procedure

May decide to do follow up PRP injections
HOW CAN WE OPTIMIZE HEALING?

Rehab Following Acute MSK Injury

Price principle
- Protection
- Relative rest
- Ice
- Compression
- Elevation

Rehab Following Orthobiologic Proc:
- Ice?
- NSAIDs?

Rehabilitation
- Immobilization?
- ROM?
- Stretching?
- Strengthening?
- Full activities?
# Lower Extremity Rehab Protocol

<table>
<thead>
<tr>
<th>Day Range</th>
<th>Activities</th>
</tr>
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<tbody>
<tr>
<td>Day 0-3</td>
<td>Protected Weight Bearing</td>
</tr>
<tr>
<td>Day 4-7</td>
<td>- Allow increased weight on joint</td>
</tr>
<tr>
<td></td>
<td>- ROM encouraged</td>
</tr>
<tr>
<td></td>
<td>- Light Cycling/ pool walking</td>
</tr>
<tr>
<td>Day 7-14</td>
<td>- Continue ROM</td>
</tr>
<tr>
<td></td>
<td>- Low grade CKC activities</td>
</tr>
<tr>
<td></td>
<td>- Continue low impact activities</td>
</tr>
<tr>
<td>Wks 2-4</td>
<td>- Increase CKC activities,</td>
</tr>
<tr>
<td></td>
<td>- Start OKC and light aerobic exercise (if pain/ swelling minimal)</td>
</tr>
<tr>
<td>Wk 4+</td>
<td>- Dynamic strengthening allowed</td>
</tr>
<tr>
<td></td>
<td>- Allow aerobic exercise as tolerated, progressing slowly</td>
</tr>
</tbody>
</table>
Insurance does not cover the procedures at this time.

There is no “national standard” for cost in the United States.
There are more than 4627 adult stem cell clinical trials approved by the US Food and Drug Administration that are currently being conducted with ongoing recruitment.

Currently considered investigational.

Coverage from insurance companies in the future?

Questions That Need to Be Answered...

- Protocol for maximum efficacy?
- Dose/type of cells for maximum efficacy?
- What is the quality of tissue that is regenerated?
- What are the most important biologic factors of a patient that can affect outcome of treatment?
- What are the long-term outcomes for some of these procedures?
SUMMARY

- Low risk procedures that are showing great potential for treatment of multiple orthopedic issues.
- There are a lot of accumulating basic science and preclinical studies supporting the benefits of stem cell therapy.
- Clinical trials demonstrating the value of these new approaches are growing.
- Many questions remain regarding dose, protocols and long term benefits of the procedures.
OTHER REFERENCES

- REVIEW - Mesenchymal stem cells in arthritic diseases. Faye H Chen and Rocky S Tuan, Arthritis Research & Therapy 2008, 10:223