Biologics in Sports Medicine

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A Glance at the Regenerative Space in Orthopaedics

Fat (adipose tissue)
Bone Marrow
Blood (PRP)
Prenatal (Amniotic Tissue)

Platelet Rich Plasma
What are we talking about?
What is it made of?

Components of blood:
- Plasma
- Red Blood Cells
- White Blood Cells
- Platelets

Plasma

Liquid component of blood that consists mainly of water.

Contains dissolved salts (electrolytes).

Plasma acts as a reservoir that can either replenish insufficient water or absorb excess water from tissues.

Platelets
Platelet Biology

- Platelets are small, anuclear cytoplasmic fragments that play an essential role in blood clotting and wound healing.
- Circulate for 7-10 days

Definition of PRP
Any level of platelets above "normal"

  - "Platelet-rich plasma is defined as the volume of the plasma fraction from autologous blood having platelet concentrations above baseline (200,000 platelets/ul)."

Developed in Spain in the 1980's
(Drs. Anitua and Sanchez)

Supersized!!!

<table>
<thead>
<tr>
<th>System</th>
<th>Volume of Blood (ml)</th>
<th>Centrifuge Time/Speed</th>
<th>First PRP Volume (ml)</th>
<th>Final Platelet Concentration compared with average</th>
<th>Activator</th>
<th>Level of Growth Factors compared with average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous Crystalloids</td>
<td>9</td>
<td>5 min/3,000 rpm</td>
<td>5.0</td>
<td>5.0x</td>
<td>None</td>
<td>PDGF-Ab, EGF, VEGF, TGF-β</td>
</tr>
<tr>
<td>Ossur Basic Crystalloids</td>
<td>9 or 15</td>
<td>First, 8 min 15 sec; Second, 15 min</td>
<td>2 or 4</td>
<td>3 or 4x</td>
<td>None</td>
<td>PDGF-Ab, EGF, VEGF, TGF-β</td>
</tr>
<tr>
<td>Ossur Basic Tissue Foundation</td>
<td>15, 15 ml</td>
<td>2 or 4</td>
<td>3 or 4x</td>
<td></td>
<td>None</td>
<td>PDGF-Ab, EGF, VEGF, TGF-β</td>
</tr>
<tr>
<td>GP5 II, Ossur Wesson, NY</td>
<td>27 or 54</td>
<td>15 ml 1,300 rpm</td>
<td>3 or 6</td>
<td>4.0x</td>
<td>Calcium</td>
<td>PDGF-Ab, EGF, VEGF, TGF-β</td>
</tr>
<tr>
<td>SmartVF, Aspire Technologies, Portland, ME</td>
<td>25 or 60</td>
<td>14 ml 1,300 rpm</td>
<td>3 or 7</td>
<td>4.0-7.0x</td>
<td>Thrombin</td>
<td>PDGF-Ab, EGF, VEGF, TGF-β</td>
</tr>
</tbody>
</table>
Methods of Concentrating Platelets

- Arthrex Double-Syringe® Autologous Conditioned Plasma (ACP) 10 cc blood/yield = 3cc product
- Biomet GPS® III Platelet Concentrate System 27cc blood/yield = 3cc product

Biometric GPS III®

Blood is drawn using provided 60mL tube and transferred into centrifugation tube.

Blood is transferred to concentrator.

Blood is centrifuged for 15min at 3200rpm.

Platelet-Rich Plasma is collected from the red port.

Platelet-Poor Plasma is removed from yellow port.

When do we use PRP?

- Treatment of various tendinopathies.
  - Achilles, peroneal, lateral epicondyle
  - Partial tendon tears
  - Plantar fasciitis
- Ligament tears (acute injury)
  - MCL
  - Ankle sprain
  - UCL
- Muscle Injuries
  - hamstring
- Augment surgical repairs
- Osteoarthritis
Histology

- Non-inflammatory angiofibroblastic tendinosis with neovascularization
- Disordered collagen scaffold
- Mucoid degeneration
- (Repetitive microinjury and healing attempts)
- No evidence of acute inflammation

Normal Pathologic


What's the problem here

- Most tendinopathies involve anatomic areas with minimal BLOOD FLOW & LOW CELL TURNOVER RATE
  - Joint spaces, ligaments & cartilage have a naturally limited blood supply
  - Muscle & tendons commonly experience decreased local blood flow following injury (e.g. rotator cuff, lateral epicondyle, Achilles, patella)
- This imbalance of Growth Factor supply & demand hinders the regenerative process

PRP thought to use the bodies own ability to heal itself

- Tendinopathies have poor healing potential
- Platelet rich therapies allow for an opportunity to utilize the body's own growth factors (GF) to improve the quality & speed of recovery from an injury.
The basics of Musculoskeletal Injury and repair

The repair response of MSK tissues:

- starts with the formation of a blood clot & degranulation of platelets
  1. This releases GF & cytokines at the site
  2. This microenvironment results in chemotaxis of inflammatory cells
  3. activation & proliferation of local progenitor cells.

Growth Factors

“Alphabet Soup”

These names you will hear are going to be playing a bigger factor in the years to come.

Industry is going to use these to enhance products

Review of Growth Factors Involved in

**Basic**
- Basic fibroblast Growth Factor (bFGF)
  - Stimulates blood vessels and cells to migrate to the site of healing.

**Insulin**
- Insulin Like Growth Factor (IGF-1)
  - Produced in cells that are injured.
  - Important to tendon healing during the inflammatory phase.

**Vascular**
- Vascular Endothelial Growth Factor (VEGF)
  - Stimulates blood vessel ingrowth during healing.
  - Plays a role in overuse injuries.
So many choices….

- WBC “rich” (Biomet, Magellan) vs. WBC “poor” (ACP, Cascade)
- How many platelets?
  - Volume (platelet, blood)
  - Cycles throughout day
- How many injections?
  - Therefor Mixed results

Obstacles

- Regulatory (FDA)
  - Minimal manipulation
- Research
  - Used in multiple indications, little data
  - Minimal level one comparative data ($$$)
- Financial
  - Considered experimental
  - Coding is inconsistent
  - Patient expense

Yet… Interest is growing
Does it work???

Can Platelet-Rich Plasma Enhance Tendon Repair?
A Cell-Culture Study

- Controlled laboratory study
- Human tenocytes from pediatric hamstrings cultured in PRP for 14 days against control
- Measured collagen, VEGF-A, TGF-B, and a bunch of other things
- Results: Up-regulation of collagen markers
- Conclusion: In human tenocyte cultures, PRP stimulates cell proliferation, total collagen production, and endogenous growth factors
- Extrapolated: PRP in tendon injuries might accelerate catabolism of tendon matrix and formation for fibrovascular callus

Extrapolated….

- Due to its success in laboratory studies, it was the subject of hundreds of clinical studies
  - Mostly Case studies, or low powered randomized studies
  - Pubmed: 8440 studies under “platelet rich plasma”
However….

- Recent studies have shown mixed results:
  - Improved recovery with hamstring injury: Shorter RTP, but no decrease in reinjury rate
  - Hamid et al AJSM October 2014
  - No significant improvement in healing of rat gastrocnemius
    - Delos et al AJSM September 2014
  - Significant decreased RTP time in high ankle sprains
    - Laver et al KSSTA June 2014

Future directions?

Comparison Between Hyaluronic Acid and Platelet-Rich Plasma, Intra-articular Infiltration in the Treatment of Gonarthrosis

Fabio Cerza,* MD, Stefano Cerri,† MD, Alessandro Cascaglia,‡ MD, Ignazio Di Vincenzo,§ MD, Valerio Schiavello,∥ MD, Andrea Piccioni,∥ MD, Giuseppe De Biasi,∥ and Michele Cuffreda†

Investigation performed at the Paolo Colombo Hospital of Verona, Verona, Italy

AJSM Dec 2012

***PRP showed a significantly better clinical outcome than HA

Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis

An FDA-Sanctioned, Randomized, Double-blind, Placebo-controlled Clinical Trial

Patrick A. Kehl,* MD

Investigation performed at the Columbia Orthopaedic Group, Columbia, Missouri, USA

- AJSM 4-2016
- N = 30
  - 15 prp, 15 saline (3 injections weekly)
- At 1 year, WOMAC scores improved
  - 78% vs 7%
- No adverse reactions
• Comparison between PRP and Viscosupplementation
• 6 studies, 739 patients
• Outcome at 6 and 12 months
• Clinical outcome and WOMAC scores significantly better between PRP and HA from 3-12 months
• Limited evidence between leukocyte poor vs rich

Viscosupplementation
• Hyaluronic acid
• Acts as lubricant and shock absorber
• Insurance covers every 6 months
• Mixed results
• However, used frequently in patients not severe enough for TKA

• PRP may act as scaffold for cartilage defect in OA
• Anabolic effect on chondrocytes, MSC
• Inhibit inflammation and alleviate OA symptoms
• ?? Anti-microbial, anti-inflammatory, anabolic
Is it Kosher???

- Legal in
  - NCAA
  - NBA
  - NFL
  - WNBA
  - NHL
  - MLB

World Anti-Doping Agency
September 2009

Local injection at the site of injury will require a declaration of use that is in compliance with the International Standard for Therapeutic Use Exemptions (TUE) from a medical professional.

*** Need a Doctor’s note
Doses of IGF-1 in PRP are subtherapeutic for anabolic effects

Conclusions

- PRP is a higher concentration of platelets
- Small studies showing earlier RTP acute in injuries
- Still need for significant research to define differences in
  - Concentration
  - Number of injections
- While mixed results in level of benefit, no adverse effects have been reported (except cost)
- Look for future studies involving OA treatment
- Patient selection!!!!!!!
Why Adipose Tissue?

- Minimally invasive harvest
- Fat is known to contain properties that may aid in healing and tissue repair
- High concentrations of reparative elements found within adipose tissue
  - 100 to 500 times more reparative cells than from an equivalent amount of bone marrow (these cells in adipose tissue are unlikely to decrease with age, as with bone marrow)
- Almost everyone is happy to donate fat 😊

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ARNOLD I. CAPLAN, PhD
Case Western University and Cleveland Clinic
"Father of the MSC": Identified and named the Mesenchymal Stem Cell in the late 1980s
Lipogems Scientific Board

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Micro-vessels are the key!
MSCs originate from cells (specifically perivascular cells) that reside on very tiny blood vessels. These micro-sized blood vessels are HIGHLY concentrated in fat!

Adipose tissue (fat) → Perivascular cells on micro-capillaries
Injury Response of a Perivascular Cell

Proposed Sequence of Change Due to Injury

Arnold Caplan, PhD (2013)

Features of LPOGEMS

Wash & Rinse: Normal saline removes inflammatory impurities such as oil and blood
Resize: Micro-fragments the tissue so that it is injectable with a small gauge needle and can be precisely injected in order to minimize necrosis
Preserves micro-architecture: Preserves the cell and tissue microarchitecture that is NATURALLY in place to create a regenerative environment and react with the tissue!

The system: wash, rinse, resize

WASTE (oil)
WASTE (blood and oil)
STERILE SALINE (100 mL bag)
Primary adipose cluster reduction
Secondary adipose cluster reduction
Indication for Use

- FDA 510(k) Clearance: Intended for the closed-loop processing of lipoaspirate tissue in medical procedures involving the harvesting, concentrating and transferring of autologous adipose tissue harvested with a legally marketed lipoplasty system.
- The device is intended for use in orthopedic surgery, arthroscopic surgery, neurosurgery, and other surgical areas.

How is it used in orthopaedics?

- Lipogems provides an optimally resized autologous adipose tissue to
- replace,
- restructure,
- cushion,
- and support
- the repair of a patient’s damaged or injured tissue, facilitating the body’s natural healing process.

What can it be used for?

- Lipogems is intended for the support and repair of soft tissue defects associated with sports injuries and degenerative damage
- In-office, clinical setting as an ALTERNATIVE to surgery
  - Patients that do not want surgery
  - Patients that are not candidates for surgery (i.e. comorbidities)
- In surgery center, operative setting as an ADJUNCT to surgery
  - In conjunction with arthroscopy
  - In conjunction with a soft tissue repair
Regulatory landscape:
Fat is a structural tissue

- Autologous
- Minimally manipulated
- Intended for homologous use
- Not dependent on the metabolic activity for its primary function

Patient and field preparation

Infiltrate Anesthetic Solution

Wait 15 minutes following infiltration before proceeding to tissue harvest
Collect lipoaspirate: approximately 3-4x final desired volume of Lipogems

Shake for at least 1 minute and wash out blood and oily residues

Stainless steel ball bearings help to fragment the tissue and saline will rinse and remove oil and blood residues from tissue.
Disclaimer

- The information presented is intended solely for the use of healthcare professionals. A physician or healthcare provider must always rely on his or her own professional clinical judgement when deciding whether to use a particular product when treating a particular patient. Lipogems does not dispense medical advice and recommends that healthcare providers be trained in the use of any particular product before using it.
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Questions?