STEM CELL AND PLATELET-RICH PLASMA FOR JOINT MANAGEMENT
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“BIOLOGICS”
- Injectable therapies that may suppress inflammation and promote regenerative pathways
- Natural products that are harvested and are used to supplement a medical process and/or the biology of healing

2018 AAOS ANNUAL MEETING
- “Explosion of mom-and-pop shops with little or no regulation”
- Retailing of biologics “is a cash business and is very expensive”
- Google “stem cell centers” - 18 million hits

2018 AAOS ANNUAL MEETING
- Study that contacted 271 of 317 centers that market directly to consumers
- Mean cost of treatment for stem cells and/or PRP was $5,156 (range $1,500-$12,000)
“BIOLOGICS”: 3 MAIN CATEGORIES

1. Endogenous growth factors- PRP
2. Cells-mesenchymal stem cells derived from bone marrow and adipose tissue and embryonic cells from embryonic tissue
3. Amniotic or placental-derived tissues

HOT TOPIC IN ORTHOPEDICS

PLATELET-RICH PLASMA (PRP)

6 FACTORS DRIVING POPULARITY OF PRP

Aggressive marketing
Consumer demand
Few regulations
Safe
Lack of effective alternatives
Some early positive data

CONSISTS OF AUTOLOGOUS BLOOD WITH A PLATELET CONCENTRATION ABOVE NORMAL BASELINE LEVEL

• DELIVERY OF GROWTH FACTORS, INFLAMMATION MODULATORS, AND CELL ADHESION MOLECULES FROM A POOL OF DEGRANULATING PLATELETS
BIOACTIVE PROTEINS

- PDGF
- INSULIN-LIKE GF I/II
- FGF

PLATELET GROWTH FACTORS AND CYTOKINES

- Stimulate extracellular matrix synthesis
- Stimulate chondrocyte proliferation
- Promote bone remodeling
- Promote wound healing
- Inhibit catabolic pathways

THOUGHT TO FACILITATE AND ENHANCE THE HEALING OF INJURED TISSUE

AUGMENT THE NATURAL HEALING PROCESS BY INCREASING THE CONCENTRATION OF THESE CYTOKINES AT THE SITE OF INJURY

AUTOLOGOUS

- SAFE
- ATTRACTIVE

MINIMALLY MANIPULATED TISSUE

AVoids REGULATORY HURDLES OF EXTENSIVE TESTING/TRIALS

WIDESPREAD USE

EFFICACY??

FDA REGULATES STEM THERAPIES: MINIMAL OVERSITE

- CRITERIA TO DETERMINE LOW-RISK
- LOW RISK DO NOT REQUIRE TRADITIONAL PRECLINICAL ANIMAL TRIALS OR PHASED CLINICAL TRIALS PRIOR TO HUMAN TREATMENT
- STRONG REGULATORY OVERSITE NOT NEEDED

FDA: LACK OF REGULATORY HURDLES BECAUSE:

Little manufacturing manipulation
Autologous with no systematic effect
Cannot combine with other products

Utilized in homologous way-original function
Bone marrow aspirates PRP
PREPARATION OF AUTOLOGOUS BLOOD
TWO STAGED CENTRIFUSION

“SOFT SPIN”
- Separates platelet-containing plasma from RBC/WBC
- 1,200-1,500 RPMs

“HARD SPIN”
- Separates plasma into platelet-rich and platelet-poor portions
- 4,000-7,000 RPMs

HETEROGENOUS PLASMA CONFIGURATIONS
- 40+ commercially available systems
- Vary in centrifugation time, initial blood volume, activating agents/techniques

TWO MAIN CATEGORIES BASED ON CELLULAR COMPOSITION

LEUKOCYTE RICH PRP: Leukocyte concentration above physiologic baseline

LEUKOCYTE POOR PRP: Leukocyte concentration below physiologic baseline

PRP SYSTEM
STUDY DESIGN IN LITERATURE
ALL USES OF PRP

- Wide heterogeneity of preparation methods
- Injection methods and frequency vary
- Difficult to compare studies

A Call for Standardization in Platelet-Rich Plasma Preparation Protocols and Composition Reporting
A Systematic Review of the Clinical Orthopaedic Literature

- Systematic review of literature looking at PRP preparation protocols and PRP composition utilized in clinical trials
- 105 trials between 2006 and 2016
Only 11 studies (10%) provided comprehensive reporting that included a clear description of preparation protocol that could be used by subsequent investigators to repeat the method.

Only 17 studies (16%) provided quantitative metrics on the composition of the final PRP product.

Current reporting does not enable comparison of PRP products being delivered to patients.
LITERATURE: STEM CELLS/PRP FOR KNEE ARTHRITIS

- Meta-analysis scanned 420 reports in literature-PRP
- Six had level III evidence or stronger
- PRP recent meta-analysis-19 higher quality investigations-7 studies good response to treatment, 4 studies reported bad response

EFFICACY OF PRP INJECTIONS IN KNEE OA: SYSTEMATIC REVIEW AND META-ANALYSIS

- Laudy et al. BJSM. 2014
- Meta-analysis: 317 studies/trials-10 meet criteria
- 6 randomized control studies, 4 observational studies

- PRP more effective for pain reduction compared with placebo at 6 months post injection
- PRP vs hyaluronic acid-significant difference in favor of PRP on pain reduction/improved function at 6 months post-injection
- Almost all trials had high risk of bias

Dia et al. Arthroscopy. 2017
- Meta-analysis of randomized control trials
- Systemic review and quantitative analysis of 10 level I randomized control studies (1069 patients)

- Compared platelet-rich plasma injections with both hyaluronic acid and saline injections for knee OA
- Similar results of PRP and HA at 6 months
- At 12 months PRP had significantly better pain relief and functional improvement than HA
- 8 of 10 level I studies had “a high risk of bias”
EFFICACY OF PRP INJECTIONS IN KNEE OA: SYSTEMATIC REVIEW AND META-ANALYSIS

- Kanchanatawan et al. *ESSKA* 2015
- 9 of 551 studies met inclusion criteria of randomized control

Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee

PRP – LEUKOCYTE POOR VS LEUKOCYTE RICH

  - Meta-analysis
  - Superior Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores in pts with leukocyte poor PRP vs Hyaluronic acid

LEUKOCYTE POOR VS RICH PRP AND OA OF KNEE

  - Prospective, randomized, double blind trial
  - Leukocyte-poor PRP compared with saline placebo injection for early bilateral knee OA

In short term outcomes, PRP injection has improved functional outcomes and improving symptoms vs HA or placebo in mild/mod knee OA.

LEUKOCYTE POOR VS RICH PRP AND OA OF KNEE

  - No difference in those treated with Leukocyte-rich PRP and hyaluronic acid
**LEUKOCYTE POOR PRP AND OA OF KNEE**
  - 78 patients/156 knees
  - 3 groups:
    1. Single PRP injection
    2. 2 PRP injections 3 weeks apart
    3. Single saline injection
  - Followed 6 months

**Significant difference (p<0.001) in favor of PRP compared to saline using VAS, WOMAC and patient satisfaction at 6 months**

**LEUKOCYTE POOR PRP AND OA OF KNEE**
  - FDA-sanctioned, randomized, double-blind, placebo controlled clinical trial
  - Leukocyte poor PRP vs saline
  - 30 pts/30 knees—series of 3 weekly injections
  - Moderate knee OA (LK grade 2-3)

**Significantly greater improvement (p<0.001) of WOMAC scores in PRP cohort throughout the study vs saline**
- 12 months after treatment PRP group improved 78% from baseline WOMAC score vs 7% placebo

**PRP INJECTIONS IN KNEE VS HYALURONIC ACID (HA)**
  - Randomized, blinded controlled with 12 month f/u
  - 96 pts 3 weekly injections PRP vs 96 patients 3 weekly injections HA
PRP VERSUS HYALURONIC ACID AND OA OF KNEE

- Feller et al. *JBJS* 2016
  - Modest clinical improvement in both groups
  - No difference between PRP and HA
  - Leukocyte Rich PRP

  - Randomized control
  - 3 weekly injections of PRP vs Hyaluronic acid
  - 192 pts with knee OA

PRP VERSUS HYALURONIC ACID AND OA OF KNEE

  - Both groups reported significant improvements in function and symptoms in all subjective scores used (p<0.0005)
  - Comparative analysis demonstrated no difference between groups at any follow-up time point

- Several Randomized control studies performed comparing efficacy of PRP with that of hyaluronic acid
  - Superior results with Leukocyte poor PRP vs Leukocyte rich
  - Majority of studies show improved outcome compared with hyaluronic acid at short-term f/u

OVERVIEW OF RESULTS OF PRP STUDIES

- Mixed data/high bias
- Variety of preparations tested
- Variety of injection frequencies tested
- Support for Leukocyte poor PRP in Early/mod OA knee
TABLE III - Grades of Recommendation for Platelet-Rich Plasma Treatment

<table>
<thead>
<tr>
<th>Condition or Procedure</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotator cuff repair</td>
<td>C</td>
</tr>
<tr>
<td>UCL injuries</td>
<td>I</td>
</tr>
<tr>
<td>Lateral epicondylitis</td>
<td>C</td>
</tr>
<tr>
<td>Hamstring injuries</td>
<td>C</td>
</tr>
<tr>
<td>ACL reconstruction</td>
<td>C</td>
</tr>
<tr>
<td>Patellar tendinopathy</td>
<td>C</td>
</tr>
<tr>
<td>Knee osteoarthritis</td>
<td>B</td>
</tr>
<tr>
<td>Achilles tendinopathy</td>
<td>C</td>
</tr>
<tr>
<td>Fracture and delayed unions or nonunion</td>
<td>E</td>
</tr>
</tbody>
</table>

*Grade A indicates good evidence (Level I studies with consistent findings) for or against recommending intervention. Grade B indicates fair evidence (Level II or III studies with consistent findings) for or against recommending intervention. Grade C indicates conflicting or poor-quality evidence (Level IV or V studies) not allowing a recommendation for or against intervention. Grade I indicates that there is insufficient evidence to make a recommendation.

AAOS GUIDELINES (2016)

CONCLUSIONS OF PRP INJECTION FOR KNEE ARTHRITIS

- Mixed data - lack of standardization among studies with regard to PRP preparation and administration
- Difficult to draw definitive conclusions from the currently available data but shows promise
- Support for Leukocyte poor PRP in Early/mod OA knee
- Insufficient Data supporting use other than knee OA

STEM CELLS
Harvard Calls for Retraction of Dozens of Studies by Noted Cardiac Researcher

Some 31 studies by Dr. Piero Anversa contain fabricated or falsified data, officials concluded. Dr. Anversa popularized the idea of stem cell treatment for damaged hearts.

OCT 15, 2018

STEM CELLS

- 1998 first human embryonic stem cell created
- Stem cells are undifferentiated cells capable of proliferation, self-renewal, and differentiation into specialized cells

STEM CELLS

- Embryonic and adult stem cells
- Adult stems cells (usually from bone marrow or adipose) differentiate into:
  - Hematopoietic stem cells (HSCs)
  - Mesenchymal stem cells (MSCs)

MESENCHYMAL STEM CELLS

- Bone marrow
- Adipose
- Umbilical cord matrix
- Potential to differentiate into cartilage, bone, tendon, and ligaments
APPLICATION OF MSCS

- Aspiration bone marrow/adipose
- Centrifuged to concentrate cells
- Placed in culture media increasing number/purity of cells
- Injection/placement of cells

FDA

- Only stem cell products actually approved by FDA are cord blood or placental remnants—typically indicated for pediatric cancer therapy
- None approved for any type of orthopedic use

FDA

- Public Health Service Act, Section 361
  - "If you are using the HCT/P (human cells, tissues, and tissue based products) that are minimally manipulated and homologous only, you can proceed without FDA approval"

AAOS 2016

RESEARCH

- Very few level I or II studies—quality of data for efficacy is poor
- No data to support its use but groundwork and guidelines being set
- Relatively safe
- AAOS: “We certainly do not have the evidence to tell our patients they can expect good outcomes”

THANK YOU!