Current Treatment of Soft Tissue Injuries and Orthobiologics

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Disclosures

- No Financial disclosures

Objectives

- Define orthobiologics
- Review FDA process
- Review Platelet Rich Plasma (PRP)
  - Science
  - Uses
- Review Stem Cells
  - Definition
  - Orthopedic uses
Orthobiologics

- Definition:
  - Biologic materials that seek to enhance musculoskeletal tissue regeneration and repair by modulating the biologic microenvironment
- Stem cells
- Platelet rich plasma
- Cartilage
- Collagen
- Bone

Orthobiologics

- Human cells, tissues, and cellular and tissue-based products (HCT/P) regulated by the FDA in the US
- Regulation divided into 3 tiers based on risk:
  - Category 1: Low risk, no manipulation or transplantation, no HCT/P oversight
    - PRP and other blood products
  - Category 2: Moderate risk, minimal manipulation, NCT/P oversight mainly for communicable disease agents
    - Dermal allograft
  - Category 3: Higher risk, cellular manipulation, requires IND, clinical trials and biologics license application
    - ACI/MACI

FDA Process

Preambles
Pre-Investigational New Drug Application meeting with FDA
Investigational New Drug Application meeting with FDA
Pre-Investigation New Drug Application meeting with FDA
Investigational New Drug Application

Investigational New Drug Application

Investigational New Drug Application

Clinical trials

Biologics License Application

FDA review for safety and efficacy; approval can be overturned

Preclinical trials

Formal safety and proof of concept studies

Analysis

Investigational New Drug Application

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Biologics Research

- > 500 clinical trials have been initiated evaluating mesenchymal stem cells
- > 180 trials for platelet rich plasma (PRP)
- However, most studies to date have been of poor design, small numbers, and of limited clinical impact

PRP

- Platelets are found in blood and contain growth factors that stimulate proliferation of local progenitors, direct cell differentiation, and modify local inflammatory responses
- Among those include: TGF-Beta, PDGF, VEGF, HGF, FGF, EGF, IGF-1

PRP is obtained from a patient’s whole blood, by centrifuge to concentrate a supra-physiologic concentration of platelets and other cytokines/chemokine
PRP
- Because this falls under HCP/T category 1, oversight only needed to determine safety of devices used to centrifuge PRP
- Does not require evidence of clinical efficacy

PRP
- No consensus on definition
- American Red Cross: $5.5 \times 10^{10}$ platelets / MLs
- No standardization on preparation
- Many things can influence the characteristics of PRP composition

PRP
- PAW Classification
  - (P) absolute number of platelets
  - (A) manner in which activation occurs
  - (W) absence or presence of white blood cells
PRP

- Types of PRP: (PAW Classification)
  - Pure PRP: low WBC (white blood count), anti-coagulated liquid
  - Leukocyte-rich PRP: high WBC, anti-coagulated liquid
  - Pure platelet-rich fibrin (PRF): low WBC, coagulated fibrin matrix
  - Leukocyte-rich PRF: high WBC, coagulated fibrin matrix.

- Considered to be an imprecise classification system currently

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Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor</td>
<td>Age, Gender, Concomitant medications (including anti-inflammatories), Nutritional status</td>
</tr>
<tr>
<td>Processing</td>
<td>Blood collection and storage conditions, Activation protocol (agent, concentration, timing), Storage</td>
</tr>
<tr>
<td>Delivery</td>
<td>Form of delivery (gel, solution), Timing of delivery in relation to solution, Timing of delivery in relation to activation, Heat factors (similar to donor factors), Injury severity</td>
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PRP devices

Currently > 17 different devices are utilized, each yielding products with different compositions and characteristics.
Therapeutic Applications for PRP

- Chronic Tendinopathy
  - Tennis elbow, Patellar tendinopathy, Achilles tendinopathy
- Acute muscle / soft tissue injury
  - Hamstring strains, UCL strain / partial tear
- Surgical augmentation
  - Meniscal repair, ACL repair, Rotator cuff repair, cartilage restoration
- OA

Questions regarding its use:
- When to administer?
- 1 injection or multiple injections?
- What type of PRP?
- What concentration of platelets and growth factors?

Contraindications for PRP

- Known platelet dysfunction or low platelets
- Hemodynamic instability (low blood pressure)
- NSAID use within 1 week
- Infection at the site
- Chronic anti-coagulation therapy (warfarin, lovenox, xarelto, etc)
- Active Cancer
Is PRP Clinically Effective?

- **Hamstrings:**
  - Reurink G1, Goudswaard GJ2, Moen MH3, Weir A4, Verhaar JA5, Bierma-Zeinstra SM6, Maas M7, Tol JL8; Dutch HIT-study Investigators.

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Is PRP Clinically Effective?

- **Tendinopathy?**

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**CASE 1**

- 54 M left elbow pain for 3 months
- Dx as lateral epicondylitis (tennis elbow)
- Initially treated with conventional methods
  - Activity modification
  - Tennis elbow strap
  - PT/OT
  - Cortisone injection (1-2)
  - PRP injection?
CASE 1

- Considering PRP injection
- Discussion with patient
  - $ because not covered by any insurance companies
  - Number of injections (1-3)
  - Avoid NSAIDS
  - Expect pain
  - Cont PT and activity as tolerated
  - Follow up 1 week for repeat eval and possibly repeat injection

Is PRP Clinically Effective?

- Rotator Cuff Repair / Surgery?
Is PRP Clinically Effective?

- Osteoarthritis of the Knee?

CASE 2

- 45 F left knee pain for > 3 months
  - Worked up and found to have moderate osteoarthritis without evidence of meniscus tear
  - Initially treated conventionally with:
    - Activity modification
    - PT/OT
    - Cortisone injection
      - Good relief however not lasting relief (i.e. one month)
    - Consider PRP?

CASE 2

- PRP for osteoarthritis of the knee
  - Studies show it can be beneficial, better than placebo
  - Discussion with patient
    - $ because not covered by any insurance companies
    - Number of injections (1-3)
    - Avoid NSAIDS
    - Expect pain
    - Risk
      - Infection, effusion
    - Cont PT and activity as tolerated
    - Follow up 1 week for repeat eval and possibly repeat injection
PRP Summary

- PRP injections are a relatively safe option for the treatment of a variety of MS conditions, when conventional treatment has failed.
- Available literature to this point is largely of poor quality, and often at high risk of bias.
- Better understanding of the specific molecular environment of each injury/condition is necessary to determine the most appropriate PRP formulation to utilize.
- No consensus in orthopedic literature in regards to use in soft tissue injuries.
- With the currently available literature, it should not be considered as a first line option in most soft tissue injuries.

Stem Cells

- Nomenclature is important!
Stem Cells

- What are stem cells?
- 3 main types
  - ESCs (embryonic stem cells)
  - MCSs (Adult stem cells)
  - iPSCs (Induced pluripotent stem cells)

Stem Cells

- Embryonic stem cells
  - Pluripotent
    - Can differentiate into any type of adult cell
    - Use is ethically controversial
    - May have increased tumorogenicity

Stem Cells

- Adult Stem Cells (MSCs)
  - More limited differentiation
  - Restricted to one germ layer
  - Reside within one organ system
  - Responsible for maintaining tissue turnover
    - Due to cell loss from injury or aging
Stem Cells

- Induced pluripotent stem cells (iPSCs)
  - 2006, Takahashi and Yamanaka
    - Induced dedifferentiation of skin fibroblasts back to cells with pluripotent potential
    - Overcomes ethical concerns of ESCs
    - Still have tumorigenicity concerns

Stem Cells

- Adult Stem Cells (MSCs)
  - Become cells of the musculoskeletal system
    - Bone, cartilage, muscle, ligament

Mesenchymal Stem Cells

- Considered an “adult stem cell” (pluripotent, not multipotent)
- Two types most applicable to orthopedic usage:
  - Adipose derived stem cells
  - Bone marrow derived stem cells (BMAC)
    - (most accessible for orthopedic applications)
MSCs

- Sources
  - First isolated from bone marrow
  - Most cells studied to date from marrow
  - Can be obtained from adipose tissue (fat cells) also
  - Studies comparing sources lack standardization

MSCs

- Preparation
  - Most effective methods for purity and modification yet to be determined

Orthopedic Applications for Stem Cells

- Cartilage injury
- Osteoarthritis
- Graft healing
- Fracture healing
Stem Cells: Contraindications

### Contraindications to BMAC

- Phlebitis (15% risk)
- Low hemoglobin (11 g/dL)
- Hypertension/medication (e.g., BP meds)
- Known coagulopathies or bleeding disorders
- Hypothyroidism
- Active use of pharmacologic blood thinners (e.g., Coumadin, Aspirin)
- Allergic reactions to local anesthetics
- Intra-articular injection at injection site within 6 weeks of BMAC procedure
- Contraindicated by medical or history of infection

MSCs

- **Augmentation of Tendon-to-bone healing**
  - Healing is critical to success of soft tissue injuries
  - *i.e.* rotator cuff repair

The Effect of Purified Human Bone Marrow-Derived Mesenchymal Stem Cells on Rotator Cuff Tendon Healing in an Athymic Rat

Ryan M. Degen, M.D., M.Sc., F.R.C.S.C., Andrew Carbone, M.D., Camila Cardillo, B.S., Jenchuan Zeng, M.D., Tony Chen, Ph.D., Andre Lebacqz, M.D., Liang Ying, B.S., Xiang-Hua Deng, M.D., and Scott A. Redo, M.D.

Improved histologic appearance and strength of repair at 2 weeks, dissipated at 4 weeks with no difference between the 2 groups.
Stem Cells

- Treatment of tendonopathy
  - Presence of pain and dysfunction with histologic tendon pathology
  - PT first line of treatment

Stem Cells in tendonopathy

**Treatment of Lateral Epicondylitis by Using Allogeneic Adipose-Derived Mesenchymal Stem Cells: A Pilot Study**

Sean Young Lee,* Wim Kei,* Cheorong Lee,* Sun G. Chong†‡

Improvement in VAS, elbow performance and defect size over 52 weeks. Concluded MSCs demonstrate therapeutic value in treating chronic lateral epicondylitis.

*Pilot Study

Ligament Injuries

- Preclinical Studies
  - Attempt to determine best environment for MSC treatment
  - Huang et al
    - Increased load to failure hypoxic MSCs vs normoxic MSCs
  - More preclinical studies needed
Meniscal Injury

Hatsushika et al
- Pig study
- meniscal regeneration was significantly better in the MSC versus the control group on histologic and MRI evaluation

Meniscal Injury

Vangsness et al
- randomized double-blind controlled trial of 55 patients receiving intra-articular injections of human MSCs with partial meniscectomies
- Improved pain scores and increased meniscal volume compared to controls

Meniscal Injury

- Current research shows promise but more work is needed
Osteoarthritis

Conclusion

- PRP
  - Safe and effective in many orthopedic soft tissue conditions
  - More standardization needed in preparation and research

- Stem Cells
  - BMAC show promise in the treatment of many orthopedic soft tissue injuries
  - Current evidence is based on animal data and preclinical studies
  - More standardization and research needed

- Neither should be a first line treatment for orthopedic soft tissue injuries.
References

References


